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Oncosurgical Management of Liver Limited Stage IV Colorectal Cancer: Preliminary Data and Protocol for a Randomized Controlled Trial

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Abstract

Background: Colorectal cancer is the fourth commonest cancer and second commonest cause of cancer-related death in the United Kingdom. Almost 15% of patients have metastases on presentation. An increasing number of surgical strategies and better neoadjuvant treatment options are responsible for more patients undergoing resection of liver metastases, with prolonged survival in a select group of patients who present with synchronous disease. It is clear that the optimal strategy for the management of these patients remains unclear, and there is certainly a complete absence of Level 1 evidence in the literature.

Objective: The objective of this study is to undertake preliminary work and devise an outline trial protocol to inform the future development of clinical studies to investigate the management of patients with liver limited stage IV colorectal cancer.

Methods: We have undertaken some preliminary work and begun the process of designing a randomized controlled trial and present a draft trial protocol here.

Results: This study is at the protocol development stage only, and as such no results are available. There is no funding in place for this study, and no anticipated start date.

Conclusions: We have presented preliminary work and an outline trial protocol which we anticipate will inform the future development of clinical studies to investigate the management of patients with liver limited stage IV colorectal cancer. We do not believe that the trial we have designed will answer the most significant clinical questions, nor that it is feasible to be delivered within the United Kingdom's National Health Service at this current time.

Introduction

Colorectal cancer is the fourth commonest cancer and second commonest cause of cancer-related death in the United Kingdom [1]. Almost 15% of patients have metastases on presentation [2]. An increasing number of surgical strategies and better neoadjuvant treatment are bringing more patients to resection of liver metastases with prolonged survival in a select group of patients who present with synchronous disease [3].

It is clear that the optimal strategy for the management of these patients remains unclear, and there is certainly a complete absence of level 1 evidence in the literature. In brief, the multidisciplinary team is faced with three potential surgical strategies: resection of the primary tumor, followed by resection of the liver metastases; resection of the liver metastases, followed by resection of the primary tumor; or simultaneous (synchronous) resection of disease at both sites in a combined operation.

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A recent systematic review identified 18 publications comparing simultaneous and staged (classic or reverse) procedures that had more than 10 patients in each group [4]. No significant difference in mortality was found between these surgical strategies; however, statistically significant differences were found in duration of operation, blood loss, length of hospital stay, and morbidity. Four publications favored the simultaneous approach in terms of cumulative duration of procedure, whereas in two there was no difference. Four publications favored the simultaneous approach as regards blood loss, and four found no significant difference. All studies that compared length of hospital stay favored the simultaneous approach. Most importantly, three publications favored the simultaneous approach in terms of morbidity [5-7], whereas 7 others did not detect any difference [8-14].

The authors of the review paper conclude that no one strategy is inferior to the others and that all of them should be considered in patients presenting with synchronous colorectal liver metastases. The clear contraindication to this approach would be those patients with a symptomatic primary tumor, for example, those that are bleeding and requiring transfusion, perforated tumors, and those obstructing or with an imminent threat of the same. The biggest question arising from these studies is whether or not it is possible to identify subgroups of patients who would benefit from one particular strategy over another, particularly if considering that those patients presenting with synchronous disease may represent a distinct biological subtype [15]. Unfortunately the evidence is lacking, with a complete absence of randomized data and multiple inadequacies in existing cohort studies. The most appropriate course of management for these patients is currently determined on an individual basis by specialty multidisciplinary teams [16]. There is, therefore, a clear need for high-quality clinical evidence to empower clinicians to adequately plan surgical management.

The prospective data available suggest it may be possible to reduce surgical morbidity with a simultaneous approach. In addition to this, there is the possibility of reducing the negative impact on quality of life (QoL) and time to resumption of normal activities by performing a single (albeit more complex) operation compared with two operations. A single operation may also confer an earlier commencement of adjuvant chemotherapy and the potential for better systemic control. Finally, the National Health Service (NHS) reference costs for surgical procedures suggest that cost is predominantly a feature of operating time, critical care admission, and length of stay. A single operation may generate a lower combined figure for all of these factors resulting in cost savings.

In light of these factors, we have undertaken some preliminary work and begun the process of designing a randomized controlled trial (RCT) and present a draft trial protocol here. We do not believe, however, that the trial we have designed will answer the most significant clinical questions, nor that it is feasible to be delivered within the UK's NHS at this current time.

Methods

Objectives of the Trial

Primary Objective

The primary objective was to establish the feasibility of conducting an RCT comparing simultaneous and staged resections in liver limited metastatic colorectal cancer.

Secondary Objectives

Secondary objectives include investigating for differences between simultaneous and staged resections with respect to surgical morbidity, disease free and overall survival, the proportion of patients in which R0 resection at both sites is achieved, and the time to commencement of adjuvant systemic therapy (if planned); cost to the NHS; QoL and return to work; and patient-reported outcome measures (PROMs; to be developed within this study).

End Points

Our primary end point is willingness of multidisciplinary teams (MDTs) to randomize patients. In addition to this, the following secondary end points will also be considered:

- Total number of (severe) surgical complications (Clavien-Dindo grade 1-5)
- Disease-free survival
- Overall survival
- Achievement of R0 resection at both sites
- Completion of planned adjuvant therapy
- Time to commencement of adjuvant chemotherapy (if planned)
- Total cost of operative treatment
- QoL
- Return to work

Patient Selection Criteria

The inclusion criteria for this study is shown in Textbox 1.

Trial Design

The trial is a two-armed phase II randomized (1:1) controlled difference trial with a parallel observational arm. Centers will decide on a participant by participant basis which arm they should be included in.

Patients meeting the inclusion criteria will be identified in the MDT meeting. The local MDT will decide whether to offer the patient the opportunity to be randomized to one of two treatment arms, or to include them in a parallel observation arm. The trial commences at the point of randomization or enrollment.

Therapeutic Regimens

Surgical Treatment Arm 1 (Staged Procedures)

Preoperative Assessment

The following should be assessed before surgery in all trial participants: Assessment of American Society of Anaesthesiologists classification; routine preoperative investigations as recommended by the National Institute for Health and Care Excellence; computed tomography (CT) of the

chest or abdomen or pelvis; contrast-enhanced magnetic resonance of the liver and positron emission tomography (PET; either combined with CT or stand-alone) as required to ensure patients meet eligibility criteria, performed up to 28 days before randomization; and a diagnostic laparoscopy may be performed at the discretion of the local unit.

Operations

Participants will undergo the first of the two-staged procedures within 2 weeks of enrollment and randomization. The choice of primary first (classic strategy) or liver first (reverse strategy) will be left to the discretion of the recruiting center and addressed in a planned descriptive subgroup analysis. Both resections will be performed within 4 months of enrollment and may be laparoscopic or open and undertaken in different institutions. In this situation, data collection will remain the responsibility of the recruiting (hepatobiliary) unit.

Primary Tumor

Standard right, extended right, left or sigmoid colectomy, and anterior resection will be performed under general anesthesia with or without stoma formation dependent upon tumor location and surgeon preference.

Liver Metastases

Intraoperative ultrasound evaluation of the liver should be performed to ensure resectability of the liver metastases. The abdomen should be explored to discover extrahepatic abdominal metastases. Suspected extrahepatic abdominal metastases should be confirmed by intraoperative biopsy. The operating surgeon will ultimately decide which procedure is to be performed.

Postoperative Procedures

Postoperative care should be provided in line with local hospital procedures.

Pathology Specimen

Surgical specimens will be transported as per local hospital protocol and reported in line with the minimum data sets for colorectal cancer and colorectal liver metastases recommended by the Royal College of Pathologists.

Formalin-fixed paraffin embedded (FFPE) blocks from the diagnostic biopsy, primary tumor at the time of resection, and colorectal liver metastasis, again at the time of resection, will be sent to the study team. Snap frozen tissue of colorectal tumor and liver metastasis, as well as normal colorectal mucosa and liver parenchyma, will also be obtained (see section on Translational Research).

Time Frames

There are three key time frames within this study. First, participant enrollment and randomization to first surgical procedure should be no more than 2 weeks. In the two-staged group, the time frame between the first and second operation should be no more than 4 months. Finally, if adjuvant chemotherapy is planned (at the discretion of the treating medical oncologist), treatment must be completed within 12 months of randomization.

Concomitant Therapy

No concomitant chemotherapy or biological therapy is permitted between the time points of randomization and completion of the surgical strategy, that is, resection at both disease sites. Given this is not logistically possible in the simultaneous arm, interoperative chemotherapy in those undergoing staged procedures would severely bias the trial. Instead, it is anticipated that the participant will proceed to the second procedure as soon as fitness permits. No other anticancer or investigational therapies are permitted while participants are engaged in this study, although participants may be enrolled on other descriptive studies.

Participants in the Observational Arm

Participants in the observational arm will undergo exactly the same interventions as those randomized, the only exception being that the staging and order of surgery will be decided by the local MDT rather than being the subject of randomization.

Textbox 1. Inclusion criteria.

- Histologically confirmed primary colorectal cancer (any T or N stage) in situ treatable with surgical resection

- Minimally symptomatic primary tumor: no radiological evidence of obstruction or perforation and hemoglobin >9 g/dL

- Computed tomography and magnetic resonance imaging and positron emission tomography–confirmed liver-limited metastatic disease (any number and distribution) which in the opinion of the local multidisciplinary team is treatable with surgical resection

- Has completed all necessary neoadjuvant therapy (systemic chemotherapy [any regimen or duration] and/or radiotherapy) for the treatment of stage IV colorectal cancer before entering the trial

- No other known primary tumor or treatment for another tumor type within the 12 months before entering the trial

- Aged 18 years or older with Eastern Cooperative Oncology Group performance status 0 to 1 and considered fit to undergo potentially curative treatment (surgery +/− chemotherapy) for their disease, including having recovered from any adverse events associated with neoadjuvant therapy.

- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

- Willing to offer written informed consent according to Good Clinical Practice Guideline of the International Conference on Harmonization and national or local regulations

- Patients can only be randomized in this trial once

- Female patients of childbearing age must be willing to utilize contraception

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Surgical Treatment Arm 2 (Simultaneous Procedure)

The treatment plan for those in the simultaneous group is identical to that described above with the exception of the surgical intervention.

The simultaneous resection of colorectal primary and liver metastases is a pure combination of the procedures previously described with the hepatic resection preceding the colorectal resection. This approach will allow the early reduction of portal pressure, followed by anesthetic manipulation of the mean arterial or central venous pressures to permit a safe colonic resection and anastomosis. Performing the procedure in this sequence also allows completion of the clean part of the operation before the potentially contaminated part.

Procedures Applicable to Both Arms

Quality Control Procedures

No specific training or accreditation of surgeons will be necessary for this study, given the well-established nature of the surgical techniques under investigation. Resection of liver metastases must be performed by a consultant hepatobiliary surgeon, and resection of the colorectal primary must be performed by a consultant colorectal surgeon. Surgeon participants will be encouraged to continue to submit data to national registries and audits, and specific elements of the pathological dataset, that is, margin positivity and total nodes harvested, will be compared both within and between groups to ensure comparable quality of surgical intervention. Exact details of surgical procedures must be recorded on the case report form.

Chemotherapy and Radiotherapy Treatment Plan

The inclusion criteria state that patients must have completed a neoadjuvant regimen in the 4 months before enrollment and randomization. Administered chemotherapy may have been purposefully preoperative or induction chemotherapy with the intent of downstaging for consideration of surgical intervention. In any case, it is anticipated that this regimen will consist of 3 months treatment with either 4 cycles of CAPOX (capecitabine, oxaliplatin) or 6 cycles of FOLFOX (folinic acid, fluorouracil, and oxaliplatin), although the exact regimen will be left to the discretion of the treating medical oncologist. An interval of 4 weeks must be left between completion of chemotherapy and the first operation. For patients with rectal cancer, it is anticipated that neoadjuvant treatment will consist of either short-course radiotherapy or long-course radiotherapy with chemosensitization. The exact details of the neoadjuvant therapy will be at the discretion of the treating oncologist.

Targeted biological therapy (eg, cetuximab, panitumumab or bevacizumab) may also have been administered in the neoadjuvant setting. If so, the standard 6-week interval between administration of bevacizmab and surgical intervention is to be observed. A planned descriptive subgroup analysis will be undertaken to examine for any bias introduced by the uncontrolled use of biologics in the neoadjuvant period.

Following safe completion of surgery at both sites, adjuvant therapy may be administered at the discretion of the treating medical oncologist. This is again anticipated to be a 3-month treatment with either 4 cycles of CAPOX or 6 cycles of FOLFOX.

Clinical Evaluation, Laboratory Tests, and Follow-Up

The principle of the follow-up and evaluation strategy is to mirror existing NHS practice so as not to further inconvenience the patient or incur additional trial costs. Data will be collected at the first postoperative review following each procedure (30 [SD 5] days). Reviews at 6 and 12 months following enrollment will be performed with reference to the patient case notes and a telephone interview. The exact same follow-up protocol will be followed for patients in both the randomized and observational arms of the trial.

Before Treatment Start

The following data will be collected upon registration:

- Demographics—Age, sex, comorbidities (cardiovascular, respiratory, neurological, endocrine)
- Primary tumor—Location, T stage, N stage, tumor grade on diagnostic biopsy
- Liver metastases—Number, mean size, distribution
- Radiology (CT or contrast magnetic resonance imaging [MRI] or PET)—Confirmation of no extrahepatic metastases
- Biochemistry and hematology—Standard hematology, renal function, liver function, carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9)
- Details of neoadjuvant chemo(radio)therapy received—number of cycles, agents administered, response evaluation (Response Evaluation Criteria in Solid Tumors v1.1, RECIST v1.1), total radiation dose
- Confirmation of meeting other eligibility criteria
- Baseline EuroQol-5D (EQ5D) and Functional Assessment of Cancer Therapy-Colorectal (FACT-C)
- Planned adjuvant therapy

During Treatment

The following data will be collected immediately following each procedure (where relevant):

- Type of colorectal resection performed
- Type of liver resection performed (plus combined local treatment)
- Operation length
- Estimated blood loss
- Transfusion
- Destination of patient following surgery (intensive therapy unit, high-dependency unit, or ward)

Follow-Up

Thirty (SD 5) Day Postoperative Review (After Every Procedure)

Patients will routinely be followed up face-to-face at 4 to 6 weeks following each surgical intervention. No specific investigations will be required. At this point, the following data will be collected (where applicable):

- Surgical complications as per Clavien-Dindo scale—details and dates of specific complications will be recorded
- Length of critical care stay

- Length of hospital stay
- Total in-hospital blood transfusion
- Pathological dataset for primary tumor—differentiation, margin positivity, nodal yield and positivity, T stage, N stage
- Pathological dataset for colorectal liver metastases—number and distribution of metastases, differentiation
- R0 resection rate
- Biochemistry and hematology—Standard hematology, renal function, liver function, CEA, and CA19-9
- EQ5D and FACT-C (following simultaneous resection and second staged procedure only)

Six (SD 1) Months Postrandomization

This review will be conducted with reference to the case notes and a telephone interview. The following data will be collected:

- Surgical complications as per Clavien-Dindo—details and dates of specific complications will be recorded
- Evidence of recurrence or death (ie, disease free survival)
- Whether adjuvant chemotherapy has been commenced, and if so, the number of days following randomization at which this occurred
- Whether the participant has returned to work, and if so, the number of days following randomization at which this occurred

The exact schedule for postoperative radiology and surveillance will not be explicitly specified within the trial protocol; rather, left to the discretion of the treating clinicians and local policy. At each clinical review within the trial, available radiology will be reviewed for evidence of recurrence. To enable an assessment of disease free survival, all patients must have at least two CT scans between the point of randomization and the end of the study.

Twelve (SD 1) Months Postrandomization (Protocol End)

Data collection at this point is an exact duplicate of the 6-month time point, with the addition of the EQ5D and FACT-C QoL questionnaires that will be administered by post. In addition, the date of completion of adjuvant chemotherapy (if applicable) will be recorded. One-to-one semistructured interviews will also be conducted at this time point.

Postprotocol Data Collection

Data registries will be reviewed annually for 5 years to establish overall survival.

Criteria Under Evaluation

Each end point will be individually and specifically evaluated as follows.

Primary End Point—Feasibility of Randomization

Feasibility of randomization is to be initially established in a pilot study.

Secondary End Points

Total (Severe) Complications

Although a number of scoring systems for operative morbidity exist, most trials are reported using the Clavien-Dindo model [17]. Although all complications represent a failure of treatment

and impact on the patient to some extent, the investigating team feel that those severe complications (Clavien-Dindo score 3-5), *that is*, requiring reintervention, represent the most significant clinical problem. This end point is defined as the total number of severe complications sustained by the patient within the study period, *which is* 12 months following randomization. It is accepted that this will represent a longer period of postoperative follow-up for those patients in the simultaneous arm of the study, but in each arm, the period of time to identify complications will be more than 6 months. The total number of complications and percentage of patients having complications within the study period will also be reported.

Disease Free Survival

Routine clinical follow-up will allow for the radiological evaluation of disease recurrence. Failure in this context is defined as local disease recurrence and/or nodal disease meeting standardized size criteria at the site of the primary tumor, recurrence of metastatic disease in the liver, occurrence of extrahepatic metastatic disease (not limited to the abdomen), and death.

Time to event is defined from the date of randomization until the date of first failure. Patients who remain disease free at the time of analysis will be censored to the date of last visit.

Overall Survival

All-cause mortality data will be obtained from national cancer registries outwith the follow-up formally described within the remit of the trial. Time from date of randomization to date of death will be analyzed. Patients still alive will be censored at the date of the last assessment.

Achievement of R0 Resection at Both Sites

Achievement of R0 resection must be agreed by the treating surgeon and the histopathologist reviewing the case with reference to both the operative findings and pathological assessment of the surgical specimen.

Completion of Planned Adjuvant Therapy

The optimal adjuvant therapy on the assumption of R0 resection at both sites and patient fitness will be documented at the time of randomization. The proportion of patients fulfilling this planned strategy within 12 months of randomization will be analyzed.

Time to Commencement of Adjuvant Chemotherapy

This end point will examine the time from the date of randomization to the date of administration of the first dose of adjuvant therapy (if planned).

Health Economics

Please see below the details of the planned evaluation under the section Health Economic Evaluation.

Quality of Life

Please see below details of the planned evaluation under the section on Quality of Life Assessment.

Return to Work

Defined as the number of days from randomization to return to full-time occupational activity after having had resection at both

sites, this end point will only apply to those in employment at the time of randomization. No alternative end point will be used for patients not returning to employment.

Statistical Considerations

Statistical Design

Sample Size

No formal power calculation has been performed for this draft protocol, which represents a pilot study primarily to establish feasibility of randomization.

Randomization and Stratification

This is an unblinded study with online registration and randomization. Three stratification factors will be used: center, colonic (cecum, ascending, transverse, descending, sigmoid) vs rectal primary, and anatomical (+/− local procedures) vs nonanatomical (+/− local procedures) liver resection.

Statistical Analysis

With respect to the other outcomes of interest, we will perform comparisons of proportions (total complications, R0 resection at both sites, completing planned adjuvant therapy) using the chi-square test, and time to event end points (disease free survival, overall survival, time to commencement of adjuvant therapy, time to return to work) will be analyzed using Kaplan-Meir methodology and compared between treatment arms using a log-rank test. Please see specific sections on QoL, Health Economics, and Translational Research for the planned analyses of these data.

Three further (descriptive) analyses are also planned to investigate potential confounders between the two arms, specifically, those patients undergoing the "reverse strategy" of staged resections, that is, liver first, differences in the proportion of patients undergoing laparoscopic resection(s), and the use of small molecular inhibitors before enrollment into the study.

Independent Data Monitoring Committee

An independent data monitoring committee appointed by the Liverpool Clinical Trials Unit will review the progress of the study.

Terms of reference, membership, meeting details, and data to be reviewed will be agreed independently before the start of the study.

Quality of Life Assessment

Rationale

QoL assessment is considered to be an important patient-centered outcome within this study given that

- Operative morbidity is known to impact negatively on patient QoL
- The study compares two different treatment modalities
- The treatment modalities have different intensity and duration

Quality of Life Instrument

PROMS are increasingly used in the NHS to report patient experience, benchmark services, and quality assure treatment. These normally consist of a global QoL scale (eg, EQ-5D) and a disease-specific questionnaire. We have selected FACT-C for the evaluation of colorectal cancer specific metrics.

In addition to this, we plan to explore the creation of a new PROM specifically targeting patients presenting with this advanced form of the tumor.

Study Design

The two questionnaires (EQ5D and FACT-C) will be administered at three discrete time points: baseline at registration, at the 30-day postoperative review following the synchronous or second staged procedure, and at 12 months following enrollment (ie, end of trial protocol).

The 30-day postoperative data will permit direct comparison of the effects of simultaneous and staged procedures on early postoperative QoL metrics. It is accepted that these will be at different time points from randomization but remains the outcome of primary interest.

The 12-month data will allow for the assessment of late postoperative complications, and being at a fixed time-point from randomization, may prove to be statistically more robust. This will however be confounded by differences between the two groups with respect to adjuvant therapy.

At least 5 (but no more than 10) patients from each arm of the study will be selected at random to participate in one-to-one semistructured interviews to identify patient-reported outcomes of interest that are not adequately described or covered in the EQ5D or FACT-C. Thematic analysis of transcripts will be qualitatively analyzed until saturation of the themes has been achieved.

Statistical Considerations

Missing data will be replaced by imputation, and all data will be normalized to baseline. QoL analysis will not be formally powered; however, it will be compared at 30 days postoperatively and 12 months postrandomization.

The FACT-C Trial Outcomes Index is a combination of the physical well-being, functional well-being, and colorectal cancer subscale, with an overall score out of 84 and will be the primary tool of interest. A clinically significant difference is considered to be four points [18] and will be assessed for using a two-sample t test (or Mann Whitney U test if not normally distributed). As well as direct group comparisons, longitudinal data will be examined by regression analysis.

Health Economic Evaluation

Preliminary work has suggested a cost difference between the two surgical approaches. Data pertaining to hospital length of stay and operative time were extracted from 3 recent clinical studies. In addition, reference costs for two patients from a hepatobiliary unit, one who underwent simultaneous resection and one staged, were obtained. Using cost data from the NHS Patient Level Information Costing System, the variable costs were weighted with respect to the cost drivers along with

procedure-specific fixed costs. The weighted cost difference for operative time was £7856.58 in the simultaneous group and £7722.89 in the staged. Length of stay costs were £3921.72 and £6271.61, respectively. Fixed costs (pharmacy, radiology, pathology, and other) totaling £505, critical care costs (£4500), and theatre consumables (£4000) were assumed to be comparable between the two approaches. The total cost for a simultaneous resection therefore was calculated at £20783.30 compared with £22999.50 for staged resections.

The two treatment arms will be analyzed for comparative cost-effectiveness using a decision analytic model taking a UK-centric decision maker's perspective. Health-related QoL data collected during the trial using EQ-5D, valued using UK population tariffs, will be used to estimate quality-adjusted survival using the standard area under the curve approach. Resource use will focus on hospital costs, including theatre, ward, and critical care, and drug costs, with the costs associated with a longer hospital stay likely to influence the results. The analysis will take the form of a cost-effectiveness analysis, with the outcome measure being the incremental cost-effectiveness ratio (ICER). Uncertainty in the model parameter values will be mitigated with probabilistic sensitivity analysis, which represents parameters using distributions, in this case using bootstrapping with in-trial data.

Subgroup analyses will be undertaken to identify patient subgroups in which the different treatment arms are more or less cost-effective than in the overall patient population.

Scenario analyses will be performed around important model parameters including the source of quality-adjusted life year estimates to compare the generic and disease-specific QoL measures and their implications for the model results. Results will be presented in the form of (1) the base case ICER, (2) ICERs for clinically relevant subgroups, and (3) a cost-effectiveness plane.

Translational Research

The study affords the opportunity to obtain a tissue set that will be of interest to the Institute of Translational Medicine at the University of Liverpool. Providing ethical approval can be obtained; samples will also be made available to other research groups on a collaborative basis.

Biopsy Strategy

Following delivery of the colorectal specimen, the proximal staple line will be incised and a linear cut made down the antimesenteric border before excising a peripheral sample (5 mm^3) of tumor using forceps and a scalpel. Following delivery of the liver specimen, an incision will be made through the resected surface to the liver metastasis, with care being taken not to breach the liver capsule; a peripheral sample (5 mm^3) of tumor will be obtained. Macroscopically normal adjacent colonic mucosa and liver parenchyma (1-2 cm from the tumor) will also obtained. All tissue sampling will be performed in the operating theatre under aseptic conditions followed by immediate stabilization in liquid nitrogen. Routine clinical samples will also be obtained as per local hospital guidelines. Samples will be stored locally in a –80°C archiving facility and transported to the University of Liverpool on completion of the study.

Outline of Translational Work

All study participants will have received neoadjuvant or preoperative chemotherapy, and the intention of the translational research arm is to identify potential predictive markers of response to this treatment.

The department of Molecular and Clinical Pharmacology at the University of Liverpool has considerable expertise in global proteomic assessment using the technique of isobaric tagging for relative and absolute quantification (iTRAQ). Response evaluation will be established using RECIST v1.1 and also tumor regression grade, with a view to planning the following investigations:

1. iTRAQ assessment of metastatic tumor to identify proteins differentially expressed in responders (partial response, complete response) and nonresponders (stable disease, progressive disease) to the pretrial neoadjuvant chemotherapy
2. iTRAQ assessment of primary tumor to correlate expression of proteins identified in 1
3. Immunohistochemical analysis of FFPE tissue to establish if the proteins identified in 1 and 2 are detectable in the up-front diagnostic biopsy, that is, to evaluate their potential as an up-front predictive biomarker of response.

If funding can be obtained, the same strategy can be implemented with exome sequencing. Beyond this, we have a panel of locally derived potential biomarkers previously identified from smaller clinical studies and *in vitro* work (quinone oxidoreductase 1, nuclear factor-like 2, acetylcholine). These will also be specifically reviewed and reported within the iTRAQ data and assayed for using standard immunoassays. All data generated from the translational arm of the study will undergo descriptive analysis only and will not influence the study design or power.

Patient Registration or Randomization Procedure

Patients will be recruited in the clinic once the multidisciplinary team ha*s* ensured that all eligibility criteria are met. Once the patient has agreed to participate, they will be registered into either the observational or randomized arms of the trial. If they are entering the randomized trial, they will be immediately randomized by means of an online database hosted on a secure website.

The following details will be collected upon registration:

- Demographics—Age, sex, comorbidities (cardiovascular, respiratory, neurological, endocrine)
- Primary tumor—Location, T stage, N stage, tumor grade on diagnostic biopsy
- Liver metastases—Number, mean size, distribution
- Radiology (CT or contrast MRI or PET)—Confirmation of no extrahepatic metastases
- Details of neoadjuvant chemo(radio)therapy received —number of cycles, agents administered, response evaluation (RECIST v1.1), total radiation dose

- Biochemistry and hematology—Standard hematology, renal function, liver function, CEA, and CA19-9
- Confirmation of meeting other eligibility criteria
- Baseline EQ5D and FACT-C
- Planned adjuvant therapy

Should all eligibility criteria be met, results of randomization will be made instantly available to permit the planning of the next intervention.

Reporting Adverse Events

Definitions

An adverse event (AE) is defined as any untoward medical occurrence or experience in a patient or clinical investigation subject that occurs following surgery or the administration of the trial medication regardless of the dose or causal relationship. This can include any unfavorable and unintended signs or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans), or a disease temporarily associated with the use of the protocol treatment (Good Clinical Practice Guideline of the International Conference on Harmonization, ICH-GCP).

An adverse drug reaction (ADR) is defined as any response to a medical product that is noxious and/or unexpected, related to any dose (ICH-GCP). Response to a medicinal product (used in the above definition) means that a causal relationship between the medicinal product and the AE is at least a reasonable possibility, that is, the relationship cannot be ruled out. An unexpected ADR is any adverse reaction for which the nature or severity is not consistent with the applicable product information (eg, Investigators' Brochure, ICH-GCP). A serious AE (SAE) is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment. An SAE that is considered related to the protocol treatment is defined as a serious ADR.

AEs and ADRs that are considered as serious are those that result in death, a life-threatening event, hospitalization, persistent significant disability or incapacity, a congenital anomaly or birth defect, or any other medically important condition (ie, important adverse reactions that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above).

Reporting Procedure

It is the responsibility of the principal investigator at each research site to report AEs to the trial steering committee. The chief investigator is responsible for onward reporting.

Ethical Considerations

Patient Protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West, and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good

Clinical Practice. The protocol will be approved by the local, regional, or national ethics committees.

Subject Identification

Participants will be identified through the hepatobiliary multidisciplinary team meetings and approached for screening if the treating team believes the eligibility criteria are likely to be fulfilled.

Informed Consent

All patients will be informed of the aims of the study, the possible AEs, the procedures and possible hazards to which he or she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It is the responsibility of the individual investigator to translate the enclosed informed consent document. The translated version should be dated and version controlled.

The translated informed consent form is part of the documents to be submitted to the ethics committee for approval. The competent ethics committee for each institution must validate local informed consent documents before the center can join the study. It is the responsibility of the local ethical committee to guarantee that the translation is conforming to the ICH-GCP guidelines.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he or she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized in the study. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on good clinical practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

Study-Specific Ethical Issues

The trial committee does not anticipate any specific concerns with the conduct of this trial. Both treatment strategies under study are currently in widespread clinical practice, although the criteria for optimum patient selection remain unclear. The follow-up design is aligned to current NHS follow-up procedures to minimize the inconvenience to the patient.

Patient and Public Involvement

Informal discussions with patients having undergone both simultaneous and staged procedures have suggested a preference for a single combined procedure, although the threshold of morbidity considered acceptable would be difficult to define. This work (alongside colleague and center questionnaires) is currently being undertaken.

The Delphi exercise from the Association of Coloproctology of Great Britain and Ireland has ranked this question as a key

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area for research [19], which was supported by the Oracle patient consultation exercise held at the Royal College of Surgeons of England [20].

Preliminary proton pump inhibitors work was conducted recently in Liverpool in anticipation of this study to help guide both the scope and construction of the study. Six semistructured one-to-one interviews were conducted by a single investigator (PS) with patients having undergone simultaneous (n=3) or staged (n=3) resections to identify factors that may have influenced their choice of oncosurgical approach. Interviews were transcribed and thematically analyzed to generate codes that were categorized into emergent themes. This thematic analysis identified four key themes: survival or oncological outcome, holistic outcome or return to function, logistical burden, and effect on carers.

Results

This study is at the protocol development stage only, and as such, no results are available. There is no funding in place for this study and no anticipated start date.

Discussion

We have presented preliminary work and an outline trial protocol which we anticipate will inform the future development of clinical studies to investigate the management of patients with liver limited stage IV colorectal cancer. We do not believe that the trial we have designed will answer the most significant clinical questions, nor that it is feasible to be delivered within the UK's NHS at this current time.

Conflicts of Interest

None declared.

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Abbreviations

ADR: adverse drug reaction
AE: adverse event
CA19-9: carbohydrate antigen 19-9
CAPOX: capecitabine, oxaliplatin
CEA: carcinoembryonic antigen
CT: computed tomography
EQ5D: EuroQol-5D
FACT-C: Functional Assessment of Cancer Therapy-Colorectal
FFPE: Formalin-fixed paraffin embedded
FOLFOX: folinic acid, fluorouracil, and oxaliplatin
ICER: incremental cost-effectiveness ratio
ICH-GCP: Good Clinical Practice Guideline of the International Conference on Harmonization
iTRAQ: isobaric tagging for relative and absolute quantification
MDT: multidisciplinary team
MRI: magnetic resonance imaging
NHS: National Health Service
PET: positron emission tomography
PROM: patient-reported outcome measure
QoL: quality of life
RCT: randomized controlled trial
RECIST v1.1: Response Evaluation Criteria in Solid Tumors v1.1
SAE: serious adverse event

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Protocol

Evaluating the Impact of a Web-Based Risk Assessment System (CareSage) and Tailored Interventions on Health Care Utilization: Protocol for a Randomized Controlled Trial

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Abstract

Background: Soaring health care costs and a rapidly aging population, with multiple comorbidities, necessitates the development of innovative strategies to deliver high-quality, value-based care.

Objective: The goal of this study is to evaluate the impact of a risk assessment system (CareSage) and targeted interventions on health care utilization.

Methods: This is a two-arm randomized controlled trial recruiting 370 participants from a pool of high-risk patients receiving care at a home health agency. CareSage is a risk assessment system that utilizes both real-time data collected via a Personal Emergency Response Service and historical patient data collected from the electronic medical records. All patients will first be observed for 3 months (observation period) to allow the CareSage algorithm to calibrate based on patient data. During the next 6 months (intervention period), CareSage will use a predictive algorithm to classify patients in the intervention group as "high" or "low" risk for emergency transport every 30 days. All patients flagged as "high risk" by CareSage will receive nurse triage calls to assess their needs and personalized interventions including patient education, home visits, and tele-monitoring. The primary outcome is the number of 180-day emergency department visits. Secondary outcomes include the number of 90-day emergency department visits, total medical expenses, 180-day mortality rates, time to first readmission, total number of readmissions and avoidable readmissions, 30-, 90-, and 180-day readmission rates, as well as cost of intervention per patient. The two study groups will be compared using the Student t test (two-tailed) for normally distributed and Mann Whitney U test for skewed continuous variables, respectively. The chi-square test will be used for categorical variables. Time to event (readmission) and 180-day mortality between the two study groups will be compared by using the Kaplan-Meier survival plots and the log-rank test. Cox proportional hazard regression will be used to compute hazard ratio and compare outcomes between the two groups.

Results: We are actively enrolling participants and the study is expected to be completed by end of 2018; results are expected to be published in early 2019.

Conclusions: Innovative solutions for identifying high-risk patients and personalizing interventions based on individual risk and needs may help facilitate the delivery of value-based care, improve long-term patient health outcomes and decrease health care costs.

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KEYWORDS

decision support techniques, algorithm, multiple chronic diseases, risk assessment, health services for the aged, emergency responders, hospitalization, patient readmission

Introduction

Globally, the population of individuals 65 years and older is increasing rapidly. Older patients have higher health care expenditures with costs usually rising after the age of 65 before peaking in the early to mid-nineties [1]. This trend of increasing health care costs has led the United States (US) Congressional Budget Office to project that net Medicare spending will increase from 3.5% of the gross domestic product (GDP) in 2014 to 5.7% of the GDP in 2039 (US $595 billion and approximately US $1.1 trillion, respectively) [2]. This has important policy implications for Medicare [3]. Recent estimates show that older patients with multiple chronic diseases contribute to the vast majority of total Medicare expenditures [4-6], most of which is due to emergency and post-acute care for chronic conditions [6]. According to the Centers for Medicare and Medicaid Services (CMS), nearly a quarter of all admissions were considered avoidable [7]. Another recent analysis which evaluated longitudinal health care utilization in older patients over a 5-year period showed that 21% (1104/5258) of all admissions in their cohort were potentially avoidable [8].

Health care utilization is unevenly distributed among Medicare beneficiaries. A study analyzing trends in Medicare spending concentration over a 30-year period showed that as Medicare spending increased from US $14.5 billion to US $295.2 billion from 1975 to 2004, the top 5% and 1% of beneficiaries accounted for 43% and 15.5% respectively of all Medicare expenditure in 2004 (US $125 billion and US $45.3 billion, respectively) [9]. Using the 2011-2012 Medicare claims data, another study by Joynt et al segmented beneficiaries into 6 potentially actionable groups [10]. This study found that the frail elderly (age ≥65 years and the presence of at least two conditions indicative of frailty) were most likely to be in the highest cost segment with their costs driven by inpatient and post-acute care services. More recently, another study divided older patients based on their health care costs (from most to least expensive) into 3 segments and organized them into a cost pyramid comprising of the following categories: top 5%, middle (6%-50%) and bottom segments (51%-100%) [11,12]. The authors examined cost data from 2010 through 2015, studying a cohort of patients going through the health care system and evaluated their health care utilization from one year to the next [12]. The study demonstrated that the middle segment represented the most expensive segment over time [12].

Currently, many health care organizations employ intensive population health management strategies which are targeted at patients in the top segment of the cost acuity pyramid to control costs. One such example is the integrated care management programs (iCMP) at Partners Healthcare that provides specialized care to high risk patients with multiple comorbid conditions [13]. Due to the finding that these high-cost patients transition to lower cost segments in subsequent years, a modified strategy is to target population health interventions at patients in the middle segment. Therefore, in this study, we evaluate the impact of CareSage, a risk assessment system, combined with personalized and timely interventions on the health care utilization and associated costs in older patients in the middle segment of the health care cost pyramid.

The primary aim of this study is to assess the impact of the CareSage risk assessment system combined with tailored interventions on the 180-day emergency department visits in a cohort of patients receiving care at a home health agency. Secondary aims include evaluating the impact of the CareSage risk assessment system and tailored interventions on the following: (1) 90-day emergency department visits, (2) 30-, 90-, and 180-day readmissions, (3) the total number of readmissions and total number of avoidable admissions, (4) total medical expenses and total expenses attributable to avoidable admissions, (5) mortality rates, and (6) time to first readmission.

Methods

Study Design

The study will be implemented as a two-arm randomized controlled trial with two study periods, namely an initial 3-month observation period followed by a 6-month intervention period. Each participant will be in the study for a total of 9 months. At the beginning of the observation period (baseline), enrolled patients will be randomized into two groups, either the intervention or control group. During the observation period, the CareSage algorithm will calibrate using patient data (from both groups) collected from a Personal Emergency Response Service (PERS) device. During the 3-month observational period, all participants will complete the baseline study assessments and will continue to receive usual care from their care providers, but no study interventions will be administered. The 6-month intervention period begins immediately after the observational period. During the intervention period, patients in the intervention group will be actively monitored by CareSage and will receive personalized interventions when flagged as "high" risk for emergency transport. Patients in the control group will receive care as usual during the intervention period. Assessments of study outcomes will be made at the end of the 9-month study period. Figure 1 shows the research design.

Figure 1. Research design, including a 3-month observation period followed by 6 months of the intervention. PHH: Partners Healthcare at Home.
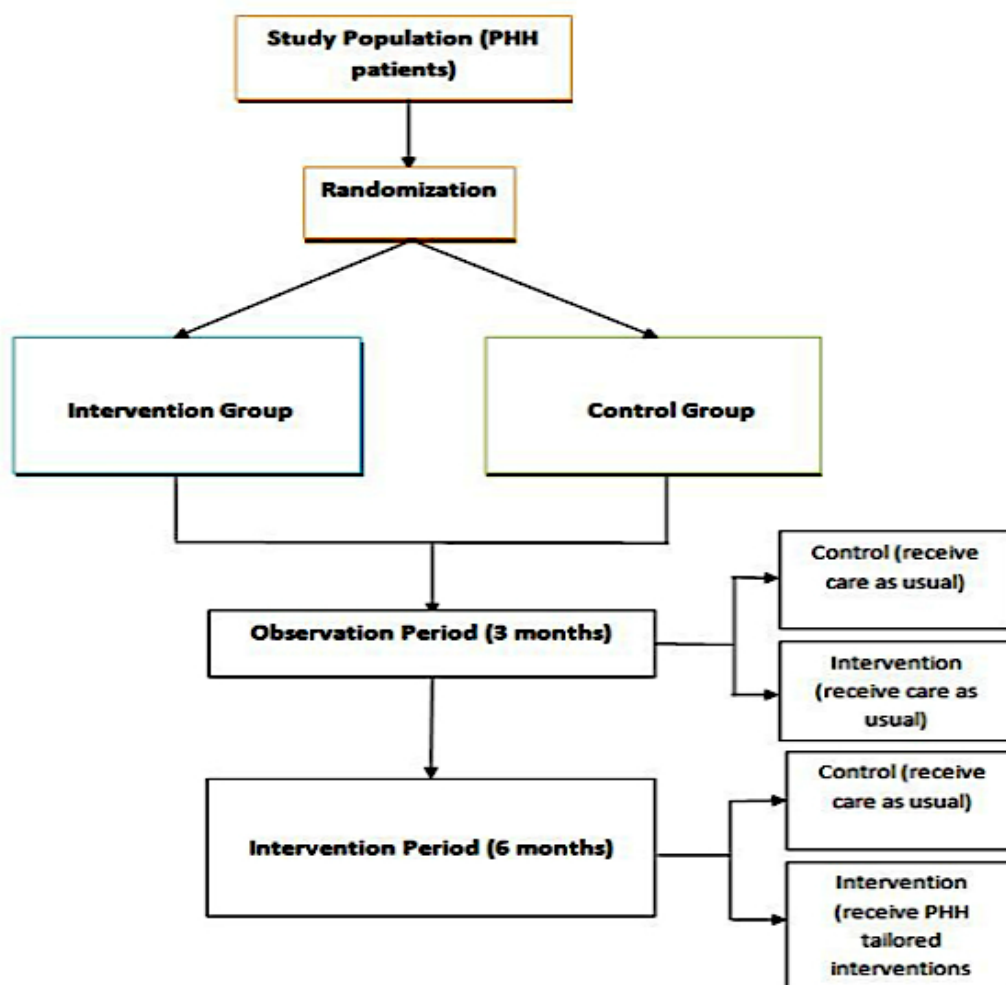
Participants

A total of 370 participants will be recruited from a pool of patients receiving care at Partners Health at Home (PHH)—a home health service that offers general care as well as specialized services to help patients manage chronic conditions. PHH consists of a network of qualified clinicians who deliver care designed to meet the unique needs of each patient, with the goal of optimizing independence and quality of life. On average, most patients are on PHH service for 2-3 months, but the duration may vary based on the patients' condition and needs. Patients who are considered likely to benefit from PHH services are typically referred to the program by their care providers. PHH services patients who are receiving care from any of the Partners Healthcare Network of hospitals (comprising of 7 major hospitals, including 2 large academic centers and several community health centers) are eligible for this study. In addition, a subgroup of patients from PHH who may be enrolled in other care management programs such as iCMP will be included in the study.

During the study, staff will periodically review previous PHH admissions and identify potential study participants. Identified patients will be prescreened over the phone to gauge interest and confirm eligibility. Eligible and interested patients will be enrolled by study staff at the patient's home. Screening,

informed consent, randomization and survey completion will occur at this enrollment visit. During this visit, patients will be given a PERS device to use for 9 months. Patients will be instructed to wear the device continuously throughout the study period.

Ethics Approval and Consent to Participate

Study was approved by the Partners Human Research Committee, the Institutional Review Board of Partners HealthCare, on 03/15/2017.

Participant Inclusion and Exclusion Criteria

Eligible participants are aged 65 years or older, English speaking patients who are receiving care or recently (within 3 months) discharged from PHH, and whose total health care costs fall within the middle 6th to 50th percentile (the middle segment of the cost acuity pyramid) of all patients seen at Partners Healthcare during the fiscal year 2016. The middle segment cutoffs for 2016 were projected based on 2011-2015 data from the analysis that was the precursor to this prospective study. Patients will not be excluded based on their disease condition as long as they fulfill the inclusion criteria stated above. Patients with artificial pacemakers and other implanted devices (as a precautionary measure against possible interference with the PERS device), currently on admission in a hospital or a

long-term-care facility including Skilled Nursing Facilities, having severe dementia, Alzheimer's disease or any other serious psychiatric illness (severe anxiety disorder or psychosis) will be excluded from this study.

Intervention

All study participants, irrespective of study group (control or intervention), will receive the following:

- A PERS device: This is a personal health technology designed to promote independent living in older adults by providing help in case of medical emergencies that lead to costly emergency department visits and hospitalizations. The PERS consists of 3 components: (1) a help push button that is worn as a necklace for 24 hours a day, (2) an in-home communication system, and (3) an emergency response center. Participants may press the help button at any time to activate the in-home communication system that connects to the response center. The response center associate enquires about the situation and contacts either an informal responder (eg, neighbor, a family member) or an Emergency Medical Service (eg, ambulance, police, or fire department) based on patient's specific situation, and then follows up to confirm that help has arrived. All participants are instructed to directly contact the Lifeline call center by pushing the PERS button or call 911 if they experience worsening of symptoms or require immediate attention. The response center associate documents the incident data and registers the situation (eg, fall, respiratory problems, chest pain, social call) and the outcome (subscriber status, responder assistance, emergency hospitalization) using proprietary software. Participants are expected to use the PERS as needed during the study period.

- CareSage: In a previous study, the medical alert pattern data captured by the PERS service was used to develop and validate a risk prediction algorithm based on the user's interaction with the device [14]. This algorithm is used by CareSage (a Web-based platform) to conduct risk assessments on patients was originally developed after studying a large cohort of the PERS subscribers (approximately 600,000) [14]. Thereafter, the algorithm was validated among a cohort (N=3335) of PHH patients to predict emergency transports in this population (area under the curve=.76). This algorithm was further refined with electronic medical records data and integrated into the health care provider-facing system (CareSage) that assesses a patient's 30-day risk for emergency transport [11]. CareSage can assess a patient's level of risk for emergency transport thereby providing an opportunity to intervene before an adverse event (emergency department visit, hospitalization) occurs. A snapshot of the provider facing Web portal is provided in Multimedia Appendix 1. CareSage is an analytics engine that builds on real-time and historical data about patients collected from both providers and Lifeline services.

Participants in the control group will receive the following:

- Passive Monitoring: These participants will continue to use the PERS system. After the 3-month observation period,

the CareSage algorithm will continue to only passively monitor control group participants but will not alert the study nurse about their risk for emergency transport. The data from CareSage will continue to be captured at the backend and will be collected at the end of the study.

- Care as usual: Participants will continue to receive medical treatment and discuss any questions or concerns with their care providers as usual. There will be no triage for control group participants.

Participants in the intervention group will receive the following:

- Active monitoring: Patients in the intervention group will be assessed by the Web-based CareSage risk assessment system, which can identify when a patient is at risk for emergency transport in any upcoming 30-day period. Patients identified as "high risk" will receive nurse triage calls and, depending on their needs, tailored interventions per a stepped-care approach (Figure 2). The principal goals of the intervention will be to address knowledge gaps in disease self-management, ensure compliance with medications and healthy diet, and identify recurrent symptoms amenable to treatment on an outpatient basis to prevent readmissions.

- Nurse Triage Call: During the intervention period, "high-risk" patients will be called by a trained study nurse to assess the physical and psychological patient's needs using a health needs assessment guide (Multimedia Appendix 2) developed by the study team. These 15-30-minute telephone calls will focus on how the patient is feeling, adherence to treatment plans, and connect the patient to any available resources (primary care physician, dietician etc) as needed.

Tailored PHH Interventions The PHH interventions consist of multiple components tailored to individual patients based on the needs identified during nurse triage call. The complete intervention decision pathway is depicted in Figure 3. There are 3 interventions that the study nurse may offer.

The first intervention is patient education where participants receive structured weekly telephone-based education sessions over the next 4-week period. In addition to the structured educational sessions, patients may receive a "just-in-time" teaching session based on the clinical judgment of the study nurse. Patient education will cover a variety of topics including diet, physical activity, importance of daily measurements, recognizing symptoms of disease, and medication adherence. The study nurse will also assess current medications and make specific recommendations to eliminate unnecessary medications and simplify the overall regimen. Structured education sessions will typically last for 30-45 minutes over a telephone call.

The second intervention is home visits. If the patient needs further intervention other than education, the study nurse may contact the patient's primary care provider (PCP) to get approval for an in-person clinical assessment. If the PCP's approval is received, then the bulk of the patient's education covering pertinent topics such as diet, activity, medications, and other topics would occur during or after the in-person clinical assessment.

Figure 2. Stepped care approach for those flagged as high risk and not flagged as high risk.
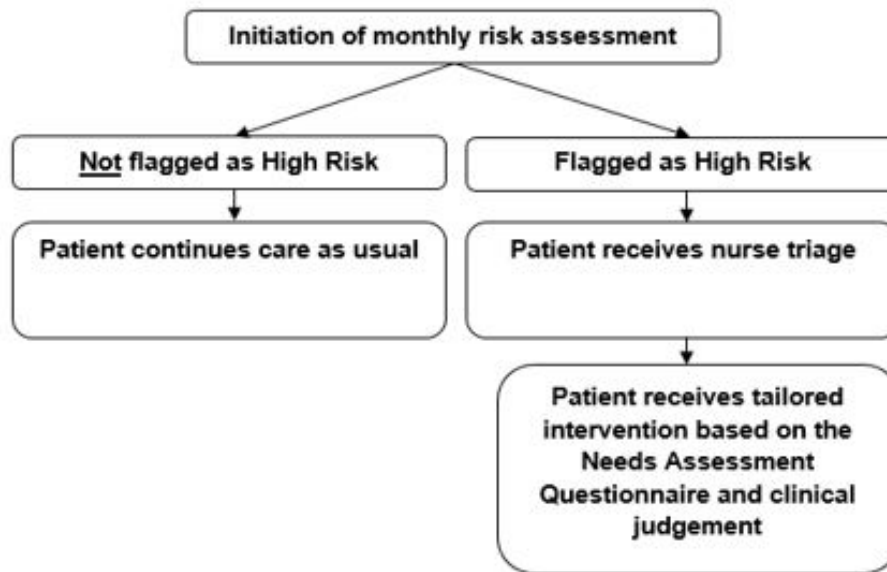
Figure 3. Details of the intervention decision pathway which includes patient education sessions, home visits, and telemonitoring support for patients classified as high risk in each 30-day assessment during the intervention period. CaU: care as usual; CS: CareSage; Pts Flag: Patients Flagged; PHH: Partners Healthcare at Home; RCT: randomized controlled trial.
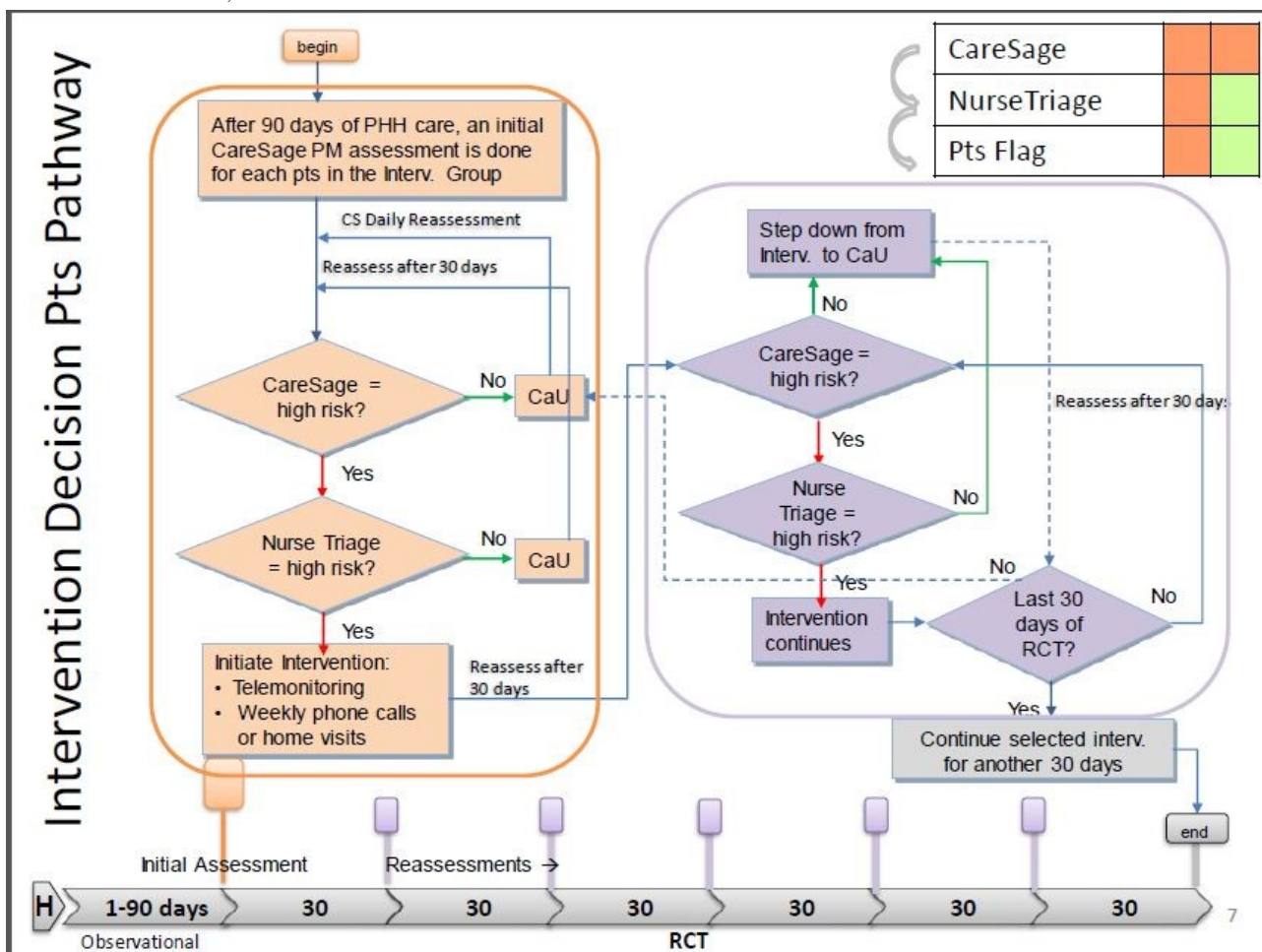
If the study nurse does not receive an approval for the in-person clinical assessment, the patient still receives basic education intervention from the nurse (as outlined above). If the PCP orders the patient to be sent to the emergency department or feels the patient needs immediate attention, the same advice will be communicated to the patient by the study nurse. In all scenarios, the PCP's decision supersedes any other study assessment.

The third and final intervention is telemonitoring support. During the phone call assessment (nurse triage), the study nurse may determine the need for telemonitoring support for a patient. Before providing telemonitoring support, the nurse will contact the patient's PCP to obtain approval. Within 3-4 business days starting from the day of PCP approval, study staff will install the telemonitoring equipment at the participants' residence with explanations on how to use the technology. The support will be maintained for a period of 4 weeks until the patient is reassessed by the CareSage algorithm. During the period of telemonitoring support, patients monitor relevant physiologic parameters (blood pressure, heart rate, weight, and blood oxygen saturation) and answer questions on heart failure-related symptoms on a touch-screen computer daily. The remote monitoring equipment includes easy-to-use devices approved by the Food and Drug Administration, namely a monitor, a digital weight scale, a blood pressure cuff and meter, and a pulse oximeter device. If the patient's PCP does not approve telemonitoring support, the patient still receives basic patient education (described above) from the study nurse. Data from these devices will be transferred securely to a remote monitoring database where the records are reviewed by the study nurse daily.

All study participants will be instructed to contact the Lifeline call center by pushing the PERS button device or call 911 directly if there is worsening of symptoms during the study period that require immediate attention.

Outcomes Measurement

The number of 180-day (6-month intervention period) emergency department visits in the intervention and control group will be measured as the primary outcome of interest for this study. Secondary outcomes will include the number of 90-day emergency department visits, the total cost of intervention provided to patients, total medical expenditure incurred during the study period (including total expenses attributable to the avoidable admissions), 180-day mortality rate, and time to first readmission. Furthermore, health care usage including emergency transport use, readmissions (30-, 90-, and 180-day), and the total number of avoidable admissions will be evaluated at the end of the study period. Following the methodology cited in Walsh et al and Segal et al, potentially avoidable admissions will be determined by analyzing the principal diagnosis ICD-9 code associated with each inpatient admission and categorizing the codes into 3 groups which are (1) those potentially avoidable in both institutional and non-institutional settings, (2) those potentially avoidable only in institutional settings, and (3) those which are not determined to be potentially avoidable [7,15].

Data Collection

All study data will be aggregated and analyzed at the end of the study period. Data will be collected at enrollment and closeout as described in Multimedia Appendix 3. Patient demographics will be collected using an enrollment questionnaire developed by the study investigators. All data pertaining to health care utilization (emergency department visits, readmissions during study period, avoidable admissions, mortality, and total medical expenditures) will be extracted from the Partners Healthcare patient databases—Enterprise Data Warehouse and the Remote

Patient Data Registry. The total cost of intervention provided to patients by PHH will be sourced from the PHH program costs. The emergency transport use data will be collected from the Phillips Lifeline database.

The Remote Patient Data Registry is a centralized clinical data warehouse that operates under Partners Research Information Services. It securely stores all data from across Partners hospital systems in one place and ensures security and confidentiality of patient information [16]. The Enterprise Data Warehouse is a single repository of clinical, operational, financial, and claims data of patients receiving care across the Partners system. The Phillips Lifeline database contains historical data such as demographics, patients' living situations and care giver network, self-reported medical conditions, and emergency transport data from the PERS device. The care-giver network information includes number of responders, the number of people who live with the patients, and persons to be notified after an emergency transport. Emergency transport data from the PERS device includes all information gathered during the interactions of the patients with the Lifeline call center associates. For all calls, the situation (eg, fall, respiratory problems, chest pain, and social call) and the outcome (eg, subscriber OK, responder assistance, and emergency hospital transport) are collected by the associate via custom-made software. All other data collected via questionnaires is stored in a secure electronic database, REDCap, which is a secure Web application for building and managing Web-based surveys and databases.

Patients meeting the initial eligibility criteria are identified through an Enterprise Data Warehouse query. The query will be written in structured query language to identify patients who meet the pre-set criteria. PHH study staff acquire a daily list of medical record numbers of newly-admitted patients, and then run the query for that distinct list of patients. The query output summarizes the patients' age, 2016 health care costs, and determines whether their health care costs place them in the middle cost acuity segment. Eligible patients will be contacted by study stuff to be enrolled into the study if interested.

Analysis

Sample Size

Based on a similar study with a comparable population by Coleman et al, which reported an odds ratio of 0.57 for 180-day hospital visits compared to matched controls, we are expecting to reduce the number of emergency department visits within a 180-day period by at least 35% in the intervention group compared to controls [17]. At 80% power and a type I error (alpha) of .05, we will need 185 participants in each of the study arms, accounting for a lost to follow-up of 15%.

Randomization

A total of 370 participants will be enrolled and randomized (via a computer program) to one of two groups (intervention group or control group) in a ratio of 1:1 (185 participants per group). Randomization will utilize random permutated blocks to optimize balance in each treatment group at any point in time during the study. Treatment allocation will be concealed in an opaque envelop that will be opened after the informed consent procedures. Neither the patient nor the members of the study

team will be aware of the treatment assignment until after randomization.

Statistical Analysis Plan

Data collected will be analyzed with data analysis (STATA, version 14) and statistical software (R, version 3.4.1). All the analyses will be conducted per the intention-to-treat principle. Descriptive statistics will be used to characterize the study sample, and we will summarize participants' characteristics by study arm. The two study groups (intervention and control) will be compared by the Student t-test (two-tailed) for normally distributed and the Mann Whitney U test for skewed continuous variables, respectively. The chi-square test will be used for categorical variables. Time to event (readmission) and 180-day mortality between the two study groups will be compared by using the Kaplan-Meier survival plots and the log-rank test. Cox proportional hazard regression will be used to compute hazard ratio and compare outcomes between the two groups. We will also conduct subgroup analyses based on enrollment in iCMP during the 6-month intervention period. Fixed and per-patient intervention costs will be calculated from PHH records. The monthly per-patient costs of health care services and out-of-pocket costs will be combined, and multivariate analyses comparing this sum (potential cost offset) for intervention versus usual care patients will be conducted.

Results

Enrollment and Study Completion

Active enrollment of participants for this trial is currently underway and the study is expected to be completed by end of 2018. The study results are expected to be published in early 2019.

Availability of Data and Material

The data that support the findings of this study are available from Partners Healthcare but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Partners Healthcare Institutional Review Board.

Discussion

Study Rationale

The goal of this study is to determine whether a risk assessment system (CareSage) combined with targeted interventions for high-risk patients can potentially decrease health care utilization and the associated costs. Population health management interventions have traditionally focused on the most expensive patients [18,19] and have not taken into consideration the dynamicity of the various costs segments as demonstrated by Niklova-Simons et al [12]. This study, however, is uniquely geared towards preventing patients in the middle segment of the cost acuity pyramid from transitioning to the higher cost segment. Furthermore, the current landscape of a rapidly aging population with multiple comorbidities presents numerous challenges to effective care management in this group. Therefore, as developed countries' populations age and the number of associated chronic health conditions increase, alternatives to hospital and institutional care are needed to optimize health care costs and improve patient outcomes [20].

Two key strategies are evaluated in this study. First, patients at high risk for emergency transport are identified using the CareSage risk assessment system, which leverages predictive analytics using remotely collected data from patients at home. Rather than targeting every patient currently in a home-based care management program or discharged from a care management program, the CareSage can identify those patients that need the most help managing their conditions. Recent studies have reported the development and validation of predictive models that can be used to systematically identify individuals at high risk for an unfavorable outcome in a hospital setting [21-23]. Such risk assessment models have great potential to inform treatment decisions and improve the quality of care delivered to patients who are receiving care at home. Thus, the CareSage risk assessment system presents a unique opportunity to efficiently allocate limited health care resources to patients that need them the most and thereby reduce costs associated with excessive use.

The second strategy is delivering targeted interventions (per established protocols) to patients identified as "high risk" by the CareSage predictive algorithm. Interventions will be adapted to fit the patient's needs with a focus on the patient's general functioning, including physical and psychological health status. Several studies have evaluated the effect of personalized multidisciplinary interventions for chronic conditions including heart failure, depression, and risk of falling in seniors [24,25]. Results showed significant reductions in health care utilization as well as improved patient quality of life. Therefore, we hope that an integrated approach to patient care management will have a significant impact on overall health care utilization and costs in older patients with multiple chronic diseases.

This study has a few limitations. First, the target population consists of English-speaking elderly patients who are receiving care from a home health care agency, thereby limiting the generalizability of the study results to other populations. The applicability of our study findings to other settings will require further investigation but, nevertheless, the findings will set the stage for future studies that could potentially target a more diverse population. Second, it might be difficult to capture data on hospitalizations that may occur outside of the Partners Healthcare network of hospitals. Capturing emergency department visits and hospitalizations outside of the Partners network is important because the study population is a high health care utilization group which is at risk for emergency transport and patients are typically taken to the nearest medical center for emergency care services. However, the Phillips Lifeline call center data and self-reported data from patients may help mitigate some of these challenges.

Conclusions

The CareSage risk assessment system provides an opportunity to identify and target interventions at patients at high risk for emergency health care utilization. The efficacy of this novel patient care approach, if proven, may present a feasible and

relatively inexpensive means to improve overall patient   outcomes and decrease costly health care utilizations.

Authors' Contributions

SA, RP, NF, SO, MNS, JB and LS designed the research. RP, NF, MNS, JB performed the statistical analyses; RP, NF, SO, SA, LS, MNS, and JB wrote the paper; SA had primary responsibility for the final content. All authors read and approved the final manuscript.

Conflicts of Interest

Philips funded the study. MS, JB, and LS work for Philips. Philips provided funding and did not play a role in the design of the study or writing of the manuscript.

Multimedia Appendix 1

Screen shot of provider-facing portal which shows risk categories for each participant.

[PDF File (Adobe PDF File), 91KB - resprot_v7i5e10045_app1.pdf]

Multimedia Appendix 2

Needs assessment questionnaire.

[PDF File (Adobe PDF File), 62KB - resprot_v7i5e10045_app2.pdf]

Multimedia Appendix 3

Data collection schedule.

[PDF File (Adobe PDF File), 24KB - resprot_v7i5e10045_app3.pdf]

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Abbreviations

CaU: care as usual
CS: CareSage
CMS: Centers for Medicaid and Medicare Services
EMR: electronic medical record
Pts Flag: Patients Flagged
GDP: gross domestic product
iCMP: Integrated Care Management Program
PCP: primary care provider
PERS: Personal Emergency Response Service
PHH: Partners Healthcare at Home

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Protocol

A Mobile Health Intervention to Reduce Pain and Improve Health (MORPH) in Older Adults With Obesity: Protocol for the MORPH Trial

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Abstract

Background: Chronic pain is a complex, age-related health issue that affects both physical functioning and quality of life. Because the impact of chronic pain is worsened by obesity and inactivity, nonpharmacological interventions that promote movement, reduce sitting, and aid in weight loss are needed to help manage pain symptoms among older adults with chronic pain.

Objective: The Mobile Intervention to Reduce Pain and Improve Health (MORPH) pilot trial aims to develop and test the feasibility and acceptability of a novel, patient-centered intervention to reduce chronic pain and improve physical functioning in older adults, leveraging the combination of telecoaching and individually adaptive mHealth tools to decrease both body mass and sedentary behavior.

Methods: MORPH comprises 2 phases, including a 1-year iterative development phase, and a 1-year pilot randomized controlled trial (RCT). During the development phase, representative participants will engage in one-on-one structured interviews and a 1-week field test. The resulting feedback will be used to guide the development of the finalized MORPH intervention package. During the second phase, the finalized intervention will be tested in a pilot RCT (N=30) in which older adult participants with chronic pain and obesity will be assigned to receive the 12-week MORPH intervention or to a waitlist control. Primary outcomes include self-reported pain symptoms and physical function.

Results: Phase 1 recruitment is ongoing as of December 2017.

Conclusions: The MORPH intervention brings together a strong body of evidence using group-based behavioral intervention designs with contemporary mHealth principles, allowing for intervention when and where it matters the most. Given the ubiquity of smartphone devices and the popularity of consumer activity and weight monitors, the results of this study may serve to inform the development of scalable, socially driven behavioral pain management interventions.

Trial Registration: ClinicalTrials.gov NCT03377634; https://clinicaltrials.gov/ct2/show/NCT03377634 (Archived by WebCite at http://www.webcitation.org/6yj0J5Pan)

Registered Report Identifier: RR1-10.2196/9712

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Introduction

Chronic pain has emerged as an urgent age-related [1] health issue, significantly impacting one's physical functioning [2] and quality of life [3], often causing individuals to withdraw from meaningful social relationships [4]. Pain is a complex health concern with symptoms that vary across the day. Whereas the long-term prescription of opioids is a common means of managing these symptoms, it has resulted in an epidemic of opioid misuse: more than 37% of drug-overdose deaths in 2013 were due to pharmaceutical opioids [5]. Finally, it is a costly disability: the annual cost of pain in the United States is nearly 30% higher than the costs of cancer and diabetes combined [6].

Similar to pain, obesity impacts the older adult population broadly such that 1 in 3 older adults is obese [7]. Unfortunately, pain becomes more common with increasing body mass index (BMI; [8]), and obesity exacerbates many of the adverse health effects of chronic pain. Obesity contributes to increased pain severity [9], with abdominal obesity nearly doubling the risk for chronic pain in older adults [10], and it negatively impacts the musculoskeletal system [11] by increasing mechanical stress on the body [12], inducing physical limitations and bodily pain. In fact, higher daily ratings of pain severity are associated with decreased physical performance in older adults [13].

The experience of pain varies across the day [14]; it is complex and multidimensional [15]. This experience is marked by an interaction between interoceptive cues and the cognitive and emotional responses that modulate the perception of pain. Pain perceptions can contribute to decrements in physical function [13] and withdrawal from physical [16] and social activities [4]; these then feed back onto both interoceptive cues, cognition, and emotion (see Figure 1). Previous evidence suggests that targeting cognitive and emotional responses can buffer the pain response [17-19], and brief mindfulness-based breathing exercises have been shown to ameliorate acute pain responses [20]. Given that chronic pain interferes with behavioral self-management [21], we expect that cueing these brief exercises (see [20]) alongside light to moderate movement at key moments (ie, before peaks in pain and affective lows; see the section titled "Individually Adaptive Content") will be instrumental in supporting lasting behavior change in this population.

We suggest that promoting light to moderate physical activity across the day will be important for improving pain and reducing weight in this population for several reasons. Long bouts of sedentary behavior (SB) negatively impact metabolic health independent of participation in moderate to vigorous physical activity (MVPA [22,23]), and intervening on SB by promoting postural shifts and the accumulation of activity across the day is effective for promoting long-term weight loss in older adults [24]. This approach to reducing SB results in a larger total volume of physical activity relative to MVPA promotion while producing fewer aversive physical sensations and is often preferable to older adults and those with compromised function [23,25]. Still, intervening on SB carries unique challenges. Individuals must be made aware of their patterns of activity across the day, and in turn must regularly apply strategies to address unhealthy patterns of sitting (ie, the presence of long, unbroken SB bouts).

Given the unique challenges faced by older adults with chronic pain, intervention strategies are needed that can provide real-time intervention content to support changes in diet and activity patterns across the day. These methods need to tailor content to individuals' daily pain experiences, bring the intervention to the participant, and help to combat social isolation. Fortunately, advances in consumer technologies—including the widespread use of smartphone and tablet devices across demographic groups [26] and increased popularity of consumer monitoring devices—for the first time facilitate this type of immersive, home-based intervention targeting sedentary and diet behaviors across the day. The purpose of the Mobile Intervention to Reduce Pain and Improve Health (MORPH) is to develop and test the feasibility of an innovative and broadly scalable theory- and evidence-driven group telecoaching and mHealth intervention that aims to reduce SB while promoting day-long movement and dietary weight loss. The MORPH intervention comprises 3 core components: (1) weekly group telecoaching sessions; (2) highly engaging weekly animated educational videos; and (3) MORPH Companion, a package of mHealth tools that together target weight loss and SB with the aim of reducing pain and enhancing physical function in overweight/obese adults with chronic pain (see Figure 2).

Figure 1. Pathways between chronic pain, sedentary behavior, and compromised physical function and health-related quality of life (HRQOL).
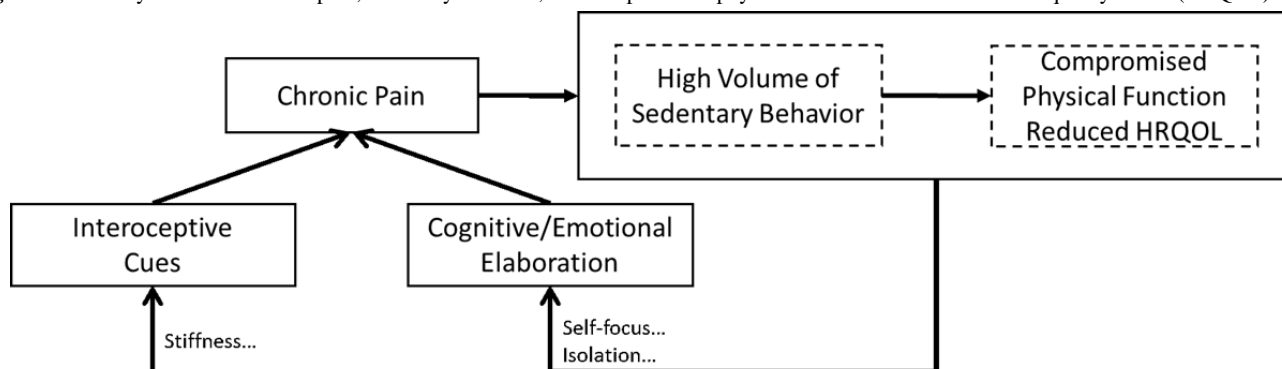
Figure 2. Key Mobile Intervention to Reduce Pain and Improve Health (MORPH) intervention components.

Weekly Group Telecoaching Sessions   Weekly Knowledge Videos   MORPH Companion   Activity Monitor   Scale

Methods

A description of the 2-phase MORPH study follows. Study protocols were reviewed and approved by a university institutional review board in February, 2018, and all participants will complete a written informed consent.

Phase I: Development of MORPH

MORPH is a 12-week weight loss and SB telecoaching intervention that is supported by the MORPH Companion mHealth package, and the content of MORPH is described in the following sections. The MORPH study will be subdivided into 2 phases. The first phase is dedicated to the development of MORPH Companion, as it is the primary vehicle of delivery for the intervention. Broadly, the design of the MORPH Companion app is grounded in social cognitive theory [27] and the Ritterband model for Internet interventions [28]. MORPH Companion will utilize a number of support and social networking features, alongside novel feedback generated using data from 2 commercially available connected health devices (ie, minute-level movement and sitting data from the Fitbit Alta

activity monitor, and daily weight data from the Aria scale; each of which will be provided to study participants). The Companion platform will be built as an embedded Web app, appearing to the user as a native app while allowing for compatibility on most mobile devices and rapid updates when necessary. The features of MORPH Companion are detailed below.

Core Components of MORPH Companion

The goal of MORPH Companion is to provide automated and fully tailored support in a package whose form and function is carefully designed alongside members of the target population, as these are key drivers of app usage within the Ritterband model [28,29]. The MORPH Companion provides immersive intervention content designed to prompt daily movement and to enhance social connections, outcome expectancies, and the participant's perceived ability to engage in valued activities, each of which are expected to influence an individual's self-efficacy (ie, one's situation-specific self-confidence), a primary determinant of behavior change (see Figure 3 [27]). As shown in Figure 4, MORPH Companion specifically targets a number of important social cognitive constructs described in the following sections.

Figure 3. Pathways between intervention support, sedentary behavior, pain, and physical function. MORPH: Mobile Intervention to Reduce Pain and Improve Health; PF: physical function; SB: sedentary behavior.
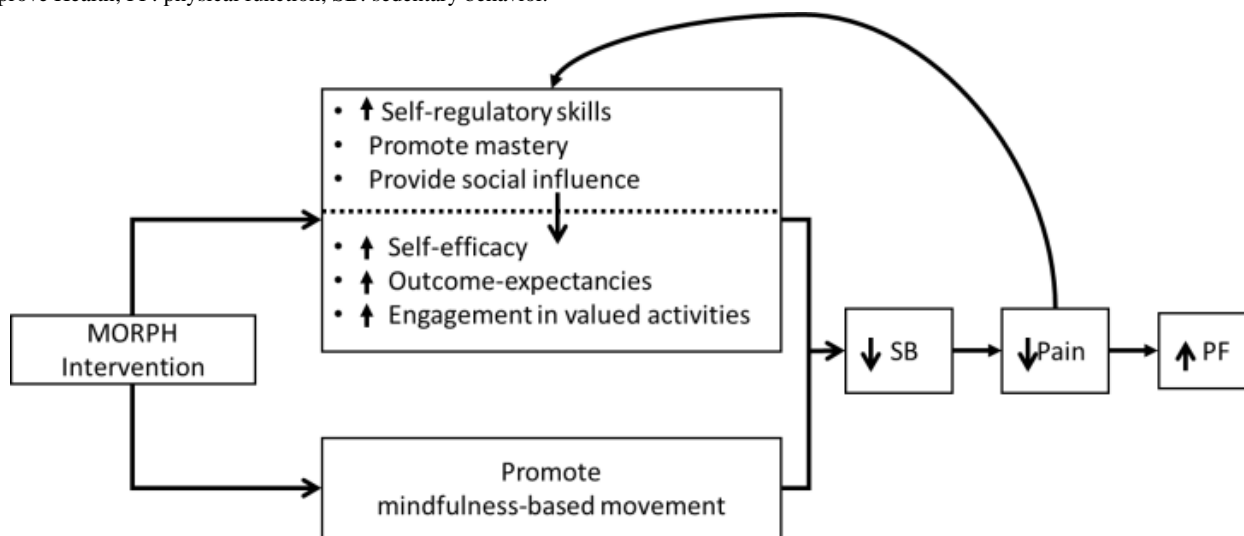
Figure 4. Technology influences on behavioral determinants. MORPH: Mobile Intervention to Reduce Pain and Improve Health.
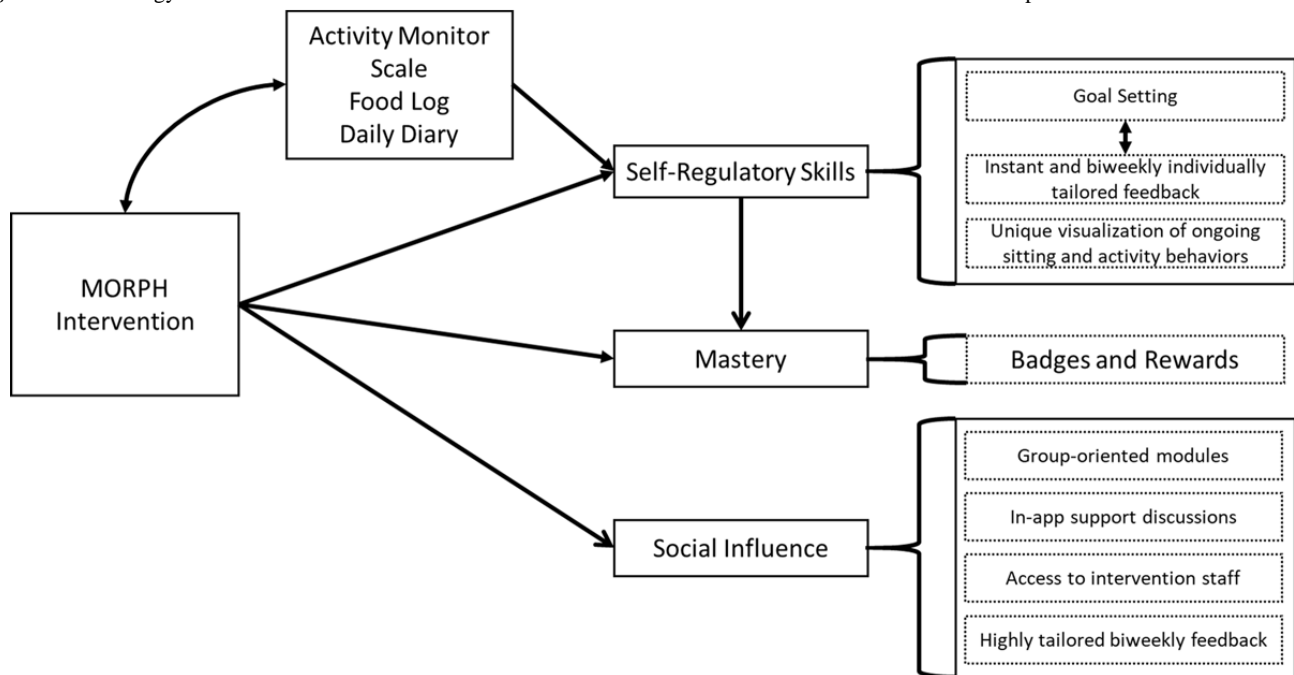
Self-Regulatory Skills

MORPH Companion integrates minute-by-minute data streams from commercially available activity monitors, as well as weight data from connected weight scales, to provide real-time visualization of daily body weight, time spent sitting, and postural shift behaviors (eg, see Figure 5). Participants will receive these devices 2 weeks before the start of the intervention, allowing for a 1-week acclimation period [30] and a 1-week baseline data collection period. These data will inform daily and weekly goals and summary feedback, which will be created automatically and then reviewed by research staff on a weekly basis. Importantly, within-day data will be utilized in "striated" sitting time feedback, displaying minute-by-minute sitting and movement behaviors on a daily timeline with the aim of providing insight into the patterns in which sitting and movement are accumulated (Figure 5). We also aim to promote physical activity across the day via *daily movement goals*. *Daily movement goals* (eg, 10,000 steps) are step goals wherein the participant is encouraged to accumulate steps throughout the day by engaging in pleasurable activities of varying intensities. To emphasize day-long movement, the *daily movement goal* is partitioned into 3 periodic movement goals (ie, morning movement, midday movement, evening movement), each allowing the participant to achieve up to 45% of the day's total goal. In this way, achieving the total movement goal requires the individual to engage in some amount of movement during each of the 3 periods.

In addition to physical activity–oriented goals, postural shift (eg, 70 sit-to-stand transitions across the day), weight (eg, a reduction of 1 pound within the next week, as assessed via the smart scale), and calorie goals (eg, a reduction of approximately 400 kcal/day from weight maintenance requirements) will be crafted or modified weekly by intervention staff and communicated to participants both via email and within the app. Activity monitor data will also be provided to staff to inform

these goals. Finally, these data will combine daily diary data, the reward system (each described below), weekly education content, and progress toward weekly goals to automatically generate weekly individualized email feedback, as previous research from our group and others has demonstrated that these regular contacts are important for sustaining app engagement and a sense of social accountability [28,29].

Reinforcement of Mastery Experiences and Progress

Setting and achieving intervention goals and receiving both real-time and weekly summary feedback will highlight mastery experiences, which act as the strongest influence on self-efficacy early in the behavior change process [27]. Additionally, our previous research [29] demonstrated that an incentive system of badges and rewards is effective for promoting app engagement and enhancing a number of social cognitive outcomes. These will be integrated throughout the app as a means of complimenting regular feedback to underscore mastery experiences. In addition to the individual goals (eg, daily postural shift goals), participants will also receive monthly group goals (eg, group cumulative step goals). Participants are instructed that achieving these goals release "mastery badges" (eg, "Bronze Stand Award"; see Figure 6), indicating successful movement on the path toward lifestyle behavior change, and they are advised to take a moment to internalize their successes. This is intended to support early and frequent mastery experiences, and in turn promote self-efficacy.

Positive Social Influence and Social Connection

Several features of MORPH Companion are designed to promote positive social influence and social connection. These include group challenge modules to foster group collaboration, such as the "Stadium Stand" (see Figure 6), which requires participants to "stand out of the 35,000 seats in the local football stadium" as a group during a 4-week period, and success is accompanied by a unique "team" badge. It is important to note that these group challenges avoid the performance-based climate

accompanying competitive "leader-board" systems that inherently highlight individual successes and failures and work against intrinsic motivation and sustained behavior [31]. Rather, they aim to foster positive social bonds and a mastery climate by providing feedback on group successes and the individual's contribution to that success. Participants will retain access to a social-networking component, wherein weekly discussion topics are provided based upon education content for that week, and participants will be encouraged to share tips and ask for advice. Finally, all participants will be able to indicate discussion content for which interventionist input is desired and will be able to reach intervention staff by phone or email throughout the intervention.

Individually Adaptive Content

Because participants' pain experiences vary across the day and between days, MORPH Companion also includes adaptive ecological momentary intervention techniques (EMI; the delivery of intervention content in real time [32]). To minimize participant burden often associated with ecological momentary assessment (EMA; the assessment of behaviors and experiences in near real-time and in the context in which they occur [32]), we will use 1-week bursts during weeks 1, 5, and 9. During each burst, participants will receive 6 brief daily assessments delivered via smartphone within 2-hour intervals throughout waking hours. To keep each assessment to a matter of seconds, participants will report only their current level of pain (on an 11-point Likert scale), affect via the Feelings Scale [33], and pain medication use since the last survey. On the first survey of the day, participants will also report the previous night's

sleep duration and quality (assessed via items from the Pittsburgh sleep quality index [34]). Prompts will be delivered via text-message, and during the development phase of MORPH, participants will be presented with 2 response options: (1) via Web app–based surveys using custom EMA software [35] or (2) the option to respond within text messages (see Figure 7). Participants will be tasked with selecting their preferred response method, which will inform the design of the intervention for the pilot randomized controlled trial (RCT; phase II). The primary function of these assessments is to identify daily risk periods: "pain peaks" and "affect troughs." We expect these 2 variables in particular to contribute to higher levels of SB and unhealthy eating [21,36]. These daily risk periods will be identified in feedback to the participant and will also be used to craft "awareness alerts." In the initial design of MORPH Companion, these 2 periods will be used to automatically generate 2 daily Fitbit alerts, each triggering a soft vibration to the wrist that will cue the participant to be mindful of their current state and to engage in light to moderate movement and brief mindfulness-based exercises—which are practiced in weekly telecoaching sessions—to improve affect, reduce pain, and prevent overeating or extended sitting. These alarms will be updated automatically with each EMA burst, with staff and participants encouraged to review and revise the timing of daily prompts. Finally, participants will complete 2 daily diary assessments (ie, upon waking, before bed) of daily pain, affect, and medication use when not within an EMA burst period. These will be used to craft feedback and to monitor changes in daily sleep behaviors and ratings of pain and affect in response to the MORPH intervention.

Figure 5. Example of "striated" sitting time feedback. Blue represents sitting; Green represents movement.
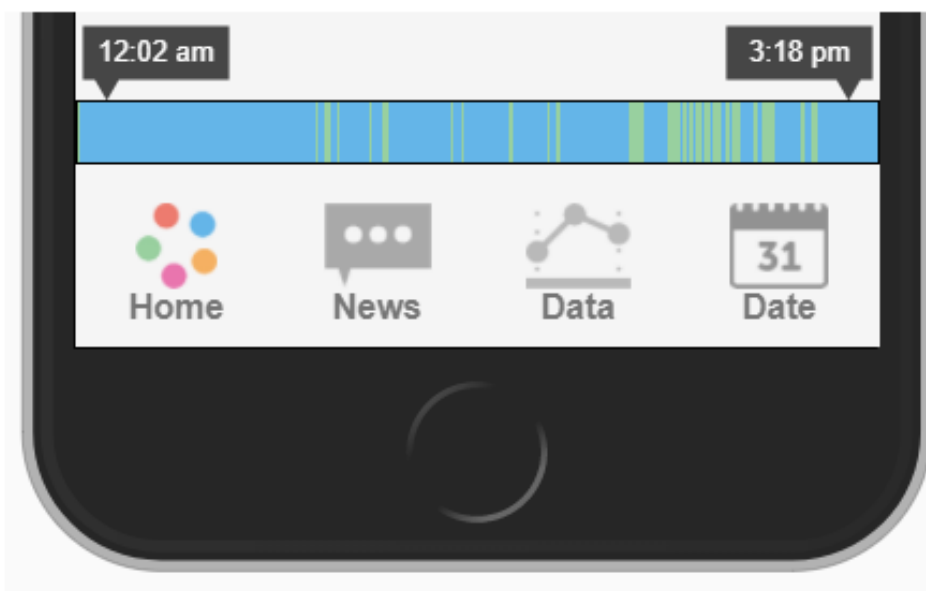
Figure 6. "Bronze Stand Award" (left) and "Stadium Stand" (right) medals.

Figure 7. Web-app and text-message ecological momentary assessment options.
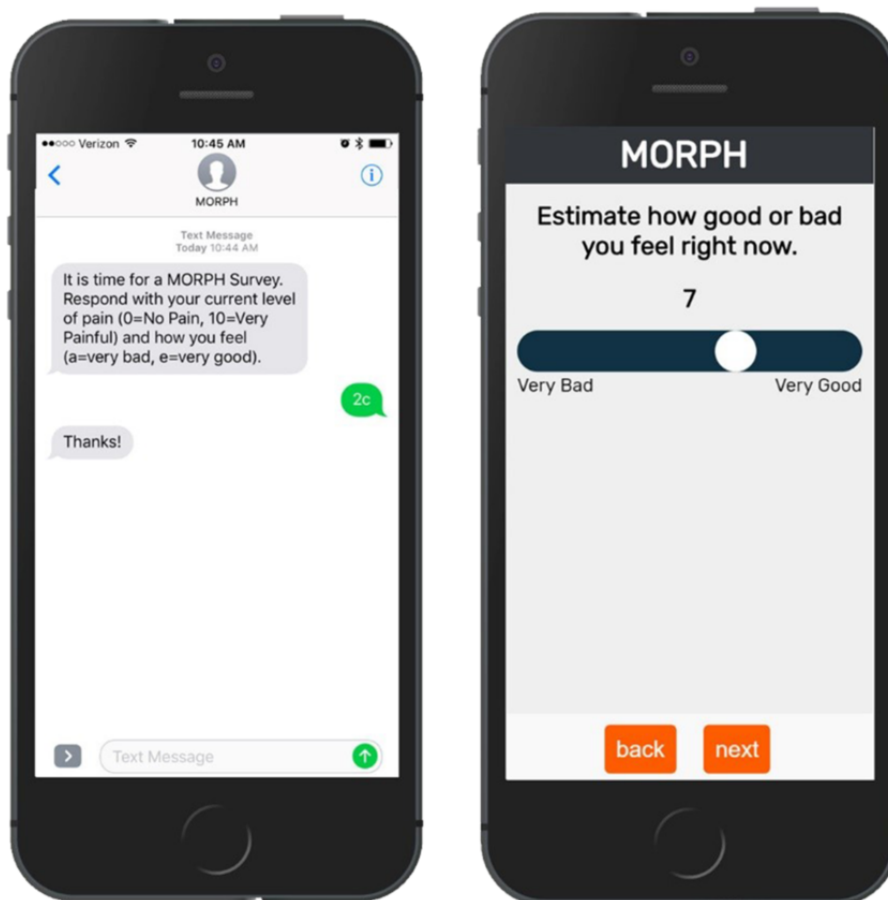
Engaging Professionally Developed Session Videos

One of the challenges of presenting material remotely is ensuring that participants engage with and understand important intervention content. To facilitate this process, MORPH will release professionally developed and highly engaging animated cartoons to reinforce and summarize content related to behavioral management of pain, the benefits of day-long movement, and healthy patterns of eating that are discussed in-depth during telecoaching sessions (see [37] for an example video). Participants will receive videos on most weeks of the study and will be encouraged to view the video before the group

telecoaching sessions. Participants will also retain access to the videos throughout the duration and following the study.

Content of Weight Loss and Sedentary Behavior Intervention

The MORPH Companion app is used within a 9-week telecoaching intervention that is prefaced by 3 weeks of 1.5-hour group sessions for a total intervention spanning 12 weeks. The 3 weeks of initial face-to-face contacts are used to (1) establish the group-mediated nature of the telephone coaching contacts, (2) create connection between group members that will be built upon via the app, (3) teach basic skills needed for successful

weight loss and reduced SB, and (4) develop competence in use of the MORPH Companion. The weight loss component targets a 3% to 5% reduction in body weight. The SB component targets (1) increasing the number of postural shifts across the day and (2) increasing the performance of valued activities related to independent living, including balance, strength, and mobility activates that will augment caloric restriction to promote weight loss and increase functional capacities as assessed by the SPPB. The distal goal of the activity component is to increase steps across the day in the range of 5000-10,000 steps based on individual abilities. Individual goals for caloric intake will be prescribed to achieve an energy deficit of approximately 400 kcal/d from daily weight maintenance energy requirements (resting energy expenditure × activity factor of 1.3 for sedentary adults). Participants will maintain either paper or digital food logs (depending on preference), and these will be submitted electronically to study staff on a weekly basis. The lowest caloric goal prescribed will be 1100 kcal/d for women and 1200 kcal/d for men. The structure of the dietary weight loss intervention is based on our extensive experience in community-based weight loss and movement trials for older adults [24,38], whereas the SB intervention is built on our published work with older adults demonstrating that improvements in daily spontaneous physical activity with the aim of reducing sitting improves weight loss and maintenance of weight loss [24]. Sessions will include nutritional education and ongoing assistance in integrating physical activities into daily life, teaching and reinforcement of pain and activity self-regulatory skills, exposure to mindfulness-based stress reduction and pain management, and strategies that optimize social connection. We selected a 12-week intervention for this pilot study for several reasons. First, based on our experience conducting behavioral trials among older adults with osteoarthritis [39], peripheral artery disease [40], and the metabolic syndrome [38,41,42] among others, we believe 12 weeks is sufficient to achieve the weight [24] and physical function [43] goals for this population. Additionally, this duration will allow for the novelty of the daily prompts to diminish, allowing for the examination of the longer-term engagement with the *MORPH* model. These data will be crucial for the design of a future large-scale randomized trial.

The MORPH Companion Design Process

Because older adults are likely to have unique needs and desires with regard to app design and functionality, a user-centered design process is essential [44]. Therefore, during the latter 9 months of the initial year of the study period, individual participants (total N=10 or until no substantive changes to the app are requested) will be recruited sequentially to participate in a Think-Aloud protocol. Participants will attend a 1:1 structured session in which they will be instructed to "act as though you are talking to yourself but loud enough for others

to hear," and to attempt to do this as continuously as possible [44,45]. Audio recordings and detailed notes will be made during each session, feedback will be discussed among team members, and modifications made to the app before the next participant completes the protocol. Audio recordings will be transcribed and coded, which will allow for tracking of changes in usability over time. Following this session, in-depth interviews will be conducted to gather information relative to desired features and preferences, and these too will be audio-recorded, transcribed, coded, discussed, and implemented. We have elected to use in-depth interviewing rather than focus groups to acquire detailed reactions to the app and desires for additional app features while reducing participant's concern for sensitivity of any shared information. Next, the participant will meet with the interventionist to receive one in-person session, including an introduction to the use of MORPH Companion. Following this orientation, participants will be asked to use the app at home for 1 week, piloting all data collection and "adaptive content" components (ie, 1 EMA burst, daily movement prompts, activity monitor wear, and scale setup). After completion of this 1-week study period, participants will return to provide initial reactions to the MORPH Companion, which will be used to refine the interface. Participants will also complete the System Usability Scale (SUS [46]), which collects perceptions of the usability of the app on 10 Likert-type questions (eg, "I found the system cumbersome to use"). The SUS will also be collected from all intervention participants completing the phase-II pilot study.

Mobile Intervention to Reduce Pain and Improve Health Phase II: The Pilot Study

During the second year of the study period (ie, phase II), we will employ a 2-group randomized controlled design in 30 obese (BMI=30-40 kg/m^2), low-active older adults with chronic pain, who will be recruited from 2 Wake Forest University Medical system pain clinics and assigned to either a 12-week mHealth+telecoaching intervention (MORPH) or a wait-list control group.

Participants

Eligible participants will own an Android or iPhone smartphone, have pain in 2 of 5 areas (ie, back, neck, shoulders, hips, knees) on most days during the previous 3 months [2,47], no contraindication for participation in physical activity and approved for participation by their physician, and will be aged 65-79 years, obese (BMI=30-40 kg/m^2, weight-stable (ie, no weight loss or gain >5% in the past 6 months), and low-active (ie, engaging in less than 2 days/week of structured physical activity for at least 20 min). Excluded individuals will be unable to walk without assistive devices or will have cognitive impairment as indicated by a Montreal Cognitive Assessment [48] score of less than 22.

Figure 8. Equation for estimating effect sizes. Y represents the primary outcomes (Short Physical Performance Battery [SPPB] score, Patient-Reported Outcomes Measurement Information System [PROMIS] pain scales); subscripts FU and BL denote measurement at week 12-week follow-up and baseline, respectively; Int represents intervention status; beta represents each regression coefficient; and epsilon represents random error.

$$Y_{FU} = \beta_0 + \beta_1 Y_{BL} + B_2 Int + covariates + \epsilon$$

Primary Outcomes for the Pilot Randomized Controlled Trial

Pain will be assessed using the 3-item PROMIS Pain Intensity Scale and the 8-item Pain Interference Scale [49]. The Pain Intensity Scale tasks participants with rating how much a person hurts on a scale of 1 (had no pain) to 5 (very severe), and the Pain Interference Scale captures the impact of pain on valued areas of an individual's life (eg, how much did pain interfere with your day-to-day activities) on a scale of 1 (not at all) to 5 (very much). Final scores on both PROMIS measures are given as T-scores on a standardized distribution such that a score of 50 (SD of 10) represents an average score within the United States. Therefore, a score of 60 would represent 1 SD worse pain than average. Physical function will be assessed using the SPPB [50]. This test of lower-extremity function consists of 4-min walk at usual pace, a timed repeated chair stand, and 3 increasingly difficult standing balance tests. Each measure is assigned a categorical score ranging from 0 (inability to complete the test) to 4 (best performance) resulting in a final score of 0 to 12.

Secondary Outcomes for the Randomized Controlled Trial

Body mass will be assessed using the same scale, which is accurate to ±100 g and calibrated weekly. In addition to activity data collected via the Fitbit device, sedentary and light activity minutes and transitions will be assessed using ActivPal activity monitors (PAL Technologies Ltd, Glasgow, UK) worn at the thigh for 7 consecutive days before the start of the study and again during week 12. We will assess the number of transitions from SB to non-SB and number of daily steps. Feasibility will be determined based upon (1) whether change in primary outcomes was observed; (2) the extent to which participants were retained in the study; and (3) the extent to which participants utilized the study application. Specifically, the participants will be asked to try to use the app daily to ensure Fitbit data have automatically synchronized and to view progress toward daily transition goals, and we will examine within-person trends in weekly app use across 12 weeks.

Analysis Plan

First, simple descriptive statistics will be utilized to evaluate usability (eg, SUS scores) and feasibility of the intervention (eg, application accesses per week throughout the study period). With regard to the phase-II pilot RCT, the analytic goals are to (1) estimate the effect size of the intervention such that the results can be used to power a future larger RCT and (2) explore appropriate methods and models for analyzing the EMA/EMI data. We plan to estimate the effect size using the generalized linear model depicted in Figure 8. Due to the small sample size, we may include important covariates (eg, gender, age) if the two arms happen to be highly imbalanced. In case covariates are used, effect sizes will be estimated using the adjusted values from the above equation. We also plan to conduct similar analyses of secondary outcomes of the RCT (eg, weight loss

and SB) using the aforementioned model, applying the appropriate model link function if the secondary outcome is not continuous. We also recognize the potential value of the intensively collected EMA data. As such, we will conduct exploratory analyses to determine if preliminary evidence supports the cross-lagged reciprocal relationship between pain and self-efficacy (Figure 2). The exploratory analysis is expected to inform the analytic plan for a future larger study.

Potential Limitations

There are 2 key limitations we will attempt to address during the design and development phase of MORPH and MORPH Companion.

Participant Burden

When possible, connected sensors are used (ie, activity monitor, scale) to passively collect data, and we are collecting EMAs in bursts to minimize assessment burden. Importantly, as we have found that tying the collection of these data to valued participant outcomes reduced perceived burden, EMA and sensor data are used to provide tailored feedback to the participant and in-app rewards and badges.

Discomfort With Technology

Although many older adults use mobile technologies, many do not. Moreover, those who do use the technology often use fewer features relative to younger populations. In this regard, we have had success with a brief but immersive orientation session that occurs when activity monitors are distributed. Participants receive a "dummy" app with all features enabled. They work with the interventionist to navigate the app's features. They receive text message prompts and complete several EMAs. This process is continued until the participant is content with their ability to access and navigate the app interface. Importantly, we aim to minimize these 2 limitations during phase I by receiving and iterating on participant feedback related to the app.

Results

Phase 1 recruitment is ongoing as of December 2017.

Discussion

Chronic pain often acts as a significant threat to an older adult's physical functioning and independent living, and traditional treatment options carry myriad risks. MORPH Companion development is underway, with recruitment beginning in March of 2018. The MORPH package brings together a strong body of evidence using group-based behavioral intervention designs with contemporary mHealth principles, allowing for intervention when and where it matters the most. Given the ubiquity of smartphone devices and the popularity of consumer activity and weight monitors, the results of this study may serve to inform the development of scalable, socially driven movement interventions.

Acknowledgments

Conflicts of Interest

None declared.

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Abbreviations

BMI: body mass index
EMA: ecological momentary assessment
EMI: ecological momentary intervention
MORPH: Mobile Intervention to Reduce Pain and Improve Health
MVPA: moderate to vigorous physical activity
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
SB: sedentary behavior
SPPB: Short Physical Performance Battery
SUS: System Usability Scale

Protocol

Effectiveness of a Combined Web-Based and Ecological Momentary Intervention for Incoming First-Year University Students: Protocol for a 3-Arm Randomized Controlled Trial

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Abstract

Background: Alcohol use among university students is common, and those who drink often choose to drink heavily (ie, 4 or more drinks per session for women or 5 or more for men). Web-based interventions (WBIs), in which students complete assessments and receive personalized feedback about their alcohol use, and ecological momentary interventions (EMIs), which use mobile devices as a method of delivering intervention information, are 2 methods that have had some success in reducing alcohol use among university students.

Objective: The aim of this study was to investigate the effectiveness of a combined WBI and EMI intervention to reduce alcohol use among university students.

Methods: The study is a 3-arm randomized controlled trial. Participants will be randomized into either a WBI+EMI condition, a WBI-only condition, or an assessment-only control. Our sample will consist of first-year university students, recruited through 5 residential colleges at the University of Otago, New Zealand. All participants will complete an online survey at baseline (ie, before Orientation Week); those in the WBI-only and WBI+EMI conditions will immediately receive personalized feedback (ie, the WBI), whereas participants in the assessment-only condition will receive no feedback. In addition, participants randomized into the WBI+EMI, but not those in the WBI-only or assessment-only groups, will receive 8 Orientation Week (2 per day on nights with large social events) and 6 academic year EMIs (delivered fortnightly). Participants in all conditions will complete brief surveys at the end of the first and second semester and report their weekend alcohol use fortnightly throughout each semester via ecological momentary assessments.

Results: The primary hypothesis is that participants in the WBI+EMI group will consume significantly fewer drinks during weekends in their first semester at university compared with WBI-only and assessment-only groups. Secondary hypotheses are that, when compared with the WBI-only and assessment-only groups, the WBI+EMI group will report consuming fewer drinks during Orientation Week, report experiencing fewer negative alcohol-related consequences after first semester, and report lower Alcohol Use Disorder Identification Test-Consumption scores following their first semester.

Conclusions: This study adds to a growing body of work investigating the utility of WBIs and EMIs in curbing alcohol consumption. In addition, the study will help to inform policy approaches aimed at curbing alcohol consumption and alcohol-related harm in university students.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12618000015246; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374104&isReview=true (Archived by WebCite at http://www.webcitation.org/6z9jRLTz6)

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KEYWORDS

alcohol drinking in college; clinical trial; smartphone; internet

Introduction

Alcohol use among university students is common, with 63% of students reporting alcohol use in the past month [1]. Of greater concern is the fact that those who drink often choose to drink heavily (ie, 4 or more drinks per session for women or 5 or more for men), with 32% of students reporting a heavy drinking session in the past 2 weeks [1]. Extensive research has highlighted that students who drink in this way experience a range of negative alcohol-related consequences, such as blackouts [2,3], risky sexual behavior [4,5], and social problems [6]. Furthermore, often due to the fact that many students live in close proximity to one another in residential colleges, students who do not themselves drink are negatively impacted by those who do (eg, unwanted sexual advances and physical aggression) [7,8].

This pattern of heavy drinking is particularly concerning for new students, many of whom increase their drinking during the transition to university [9]. Indeed, researchers tend to find that the beginning of the academic year is characterized by high levels of alcohol use [10-14]. One factor that contributes to this increase in alcohol use is Orientation Week (a.k.a., Frosh, Freshers' Week, Introductory Week) [14-16]. Orientation Week generally precedes the start of the academic year and includes a number of university-organized social events that help first-year students form new friendships. Although the purpose of orientation is well intentioned, research on Orientation Week from one university suggests that new students double their drinking relative to a typical week before university [14], experience 5 times as many negative alcohol-related consequences [17], and pregame before attending the social events (ie, consume alcohol *before* attending the event) [18,19].

Web-based interventions (WBIs), where students are screened and provided with personalized feedback about their alcohol use, have been suggested as a potential means of reducing alcohol use and present a cost-effective way of reaching large numbers of individuals [20-24]. WBIs are effective in reducing alcohol use [25-27] and may be successful in reducing the likelihood of nondrinking students initiating drinking [28]. The effect, however, tends to be small [25,26]. For example, a large WBI implemented in 7 of 8 universities in New Zealand with 17- to 24-year-old students in the middle of first semester did not reduce the frequency with which students consumed alcohol but did result in a small reduction in the amount of alcohol consumed during a typical drinking session [29,30].

The generally small effect size reported for WBIs may be due to the fact that they rely on students remembering the intervention information. Furthermore, WBIs rely on advice given in a likely nonsocial context (eg, sitting in one's room completing the WBI) to transfer to a social context (eg, hanging out and having drinks with friends), neglecting the fact that social factors play a strong role in students' drinking behavior [14,17,31-35]. Ecological momentary interventions (EMIs), which use mobile devices as a method of delivering intervention information, provide a way to extend WBIs beyond the initial treatment context, not only providing individuals with reminders about the information they were given in the WBI but also a cue to apply that information in a real-world setting [36,37]. By receiving reminders close in time to the actual behavior (eg, immediately before or during a night out drinking), EMI messages can facilitate self-management of drinking in context [37].

To date, 2 pilot studies provide some support for the efficacy of EMI messages during Orientation Week [15,38]. For example, in a pilot study, first-year students were randomized into an assessment-only condition or an EMI condition. Those in the assessment-only condition reported their drinking during Orientation Week and weekly during the academic year via ecological momentary assessments (EMAs), whereas those in the EMI condition reported their drinking and received daily EMI messages during Orientation Week. The EMI messages were sent at 7:30 PM (about the time students report drinking during Orientation Week), and the content of the messages alternated between the potential health-related and social consequences of alcohol use. The initial pilot found that women (but not men) in the EMI condition consumed significantly fewer drinks than women in the assessment-only condition during both Orientation Week (17 vs 26) and weekly during the academic year (5 vs 8) [38]. Following a series of focus groups with pilot study participants, the EMI was adapted so that messages were only sent on nights with large social events and 2 messages, rather than 1, were sent on these nights. When testing these changes in a second pilot-experimental study, students attending a relatively light drinking residential college consumed significantly fewer drinks relative to an assessment-only group during both Orientation Week (10 vs 16) and a typical academic year weekend (4 vs 7). The EMI, however, had no effect on students attending a residential college with a heavier preuniversity drinking pattern during either Orientation Week (38 vs 37) or the academic year (11 vs 9) [15]. Although these preliminary findings are promising, they have only been successful at reducing lighter drinkers' alcohol use, suggesting that an EMI alone may not be not effective for all incoming students.

Recently, researchers have shown some preliminary success when using an EMI to supplement an in-person intervention or WBI [36,39-41]. For example, Haug et al [39] found that Swiss students attending vocational training schools who received a combined WBI and EMI reduced their prevalence of heavy drinking sessions compared with an assessment-only group. Similarly, Tahaney et al [40] found that risky drinking

undergraduates who received a WBI+EMI consumed fewer weekend drinks compared with those who only received a WBI-only or an assessment-only condition. Building on these earlier studies, this protocol outlines a large-scale long-term randomized controlled trial (RCT) to test a WBI+EMI intervention for incoming first-year university students.

Methods

Study Design

The study is a 3-arm RCT. Participants will be randomized into either a WBI+EMI condition, a WBI-only condition, or an assessment-only condition (Figure 1). The WBI will be administered before the start of Orientation Week, whereas the supplemental EMI will be delivered in 2 phases: 8 messages over 4 days during Orientation Week, and 6 messages during first semester. Participants will complete surveys at baseline (before Orientation Week) and after their first (~4 months) and second semester (~8 months).

Ethics Approval and Consent to Participate

This research was approved by the University of Otago Human Ethics Committee New Zealand. Participants were presented with the information sheet and consent form at the start of the online survey.

Trail Status

At the time of submission, the recruitment phase had begun but not completed. Data collection for the primary outcome will be completed in June 2018. Data collection for the secondary outcomes will be completed in November 2018.

Availability of Data and Material

All data and material supporting our findings can be obtained from the last author.

Objectives and Hypotheses

The aim of the study was to test the effect of a WBI+EMI among incoming first-year students in New Zealand. The primary hypothesis was that participants in the WBI+EMI group will consume significantly fewer drinks during weekends in their first semester at university compared with those in WBI-only or assessment-only groups. Secondary hypotheses are that, when compared with those in the WBI-only and assessment-only groups, participants in the WBI+EMI group will report consuming fewer drinks during Orientation Week, and report experiencing fewer negative alcohol-related consequences, report lower Alcohol Use Disorder Identification Test-Consumption (AUDIT-C) scores, and less typical week alcohol use (at both 4 and 8 months follow ups). We also hypothesize that those in the WBI-only condition will consume significantly fewer drinks during weekends in their first semester at university, report consuming fewer drinks during Orientation Week, report experiencing fewer negative alcohol-related consequences, and report lower AUDIT-C scores compared with participants in the assessment-only group.

Participants and Procedures

All incoming students who are beginning their first-year at university, are between 18 and 25 years, and living in any of the 5 residential colleges at the University of Otago will be invited to take part. The invitation email will be sent out from each of the residential colleges to their incoming cohorts. The initial email invitation will be sent 4 weeks before the first day of Orientation Week, with a follow-up reminder 2 weeks before the beginning of Orientation Week. Residential colleges will also invite students to take part by posting on their respective Facebook pages. Participants will be offered NZ $100 (US $73.12, Can $92.29, Aus $93.81, UK £51.56) remuneration for taking part in the study.

Participants who are interested in taking part will click a link to a secure webpage with information about the study and consent forms. Participants will be excluded if they decline to participate throughout the academic year or do not provide a mobile number. After completing the baseline survey (which includes a definition of a New Zealand standard drink), those who provide a mobile phone number will then be randomized into 1 of the 3 conditions (ie, WBI+EMI, WBI-only, and assessment-only). Participants randomized into the WBI+EMI condition and the WBI-only condition will automatically receive personalized feedback (ie, the WBI) based on their answers on the baseline survey. Participants randomized into the assessment-only group will not receive feedback.

Participants randomized into the WBI+EMI condition, but not those in the WBI-only condition or assessment-only condition, will receive EMIs during Orientation Week and throughout the first semester. Participants in all conditions will be asked to report their alcohol use during Orientation Week and fortnightly throughout the academic year via EMAs (ie, text messages) and complete brief surveys at the end of the first and second semester. Reimbursement will occur at the end of the academic year.

Assessment and Outcome Measures

The primary outcome measure will be weekend alcohol use during first semester, reported via fortnightly EMAs. Secondary outcomes will include Orientation Week alcohol use, alcohol-related consequences, AUDIT-C scores, and typical weekly alcohol use (measured at baseline, after semesters 1 and 2).

Measures

Demographics

Demographic variables (age, gender, ethnicity) will be assessed at baseline.

Academic Year Weekend Alcohol Use

Academic year weekend alcohol use [14,15] will be assessed by fortnightly EMAs during semesters 1 and semester 2 of a students' first year at university ("How many drinks did you have Thurs, Fri, Sat? Send reply like this: 1,5,0."; see Table 1). This procedure has been used in prior studies with good compliance (75% completed 4 or more of the 7 academic year reports in the pilot study) [13,14].

Figure 1. Flow of events. AUDIT-C: Alcohol Use Disorder Identification Test-Consumption; EMI: ecological momentary intervention; WBI: Web-based intervention.
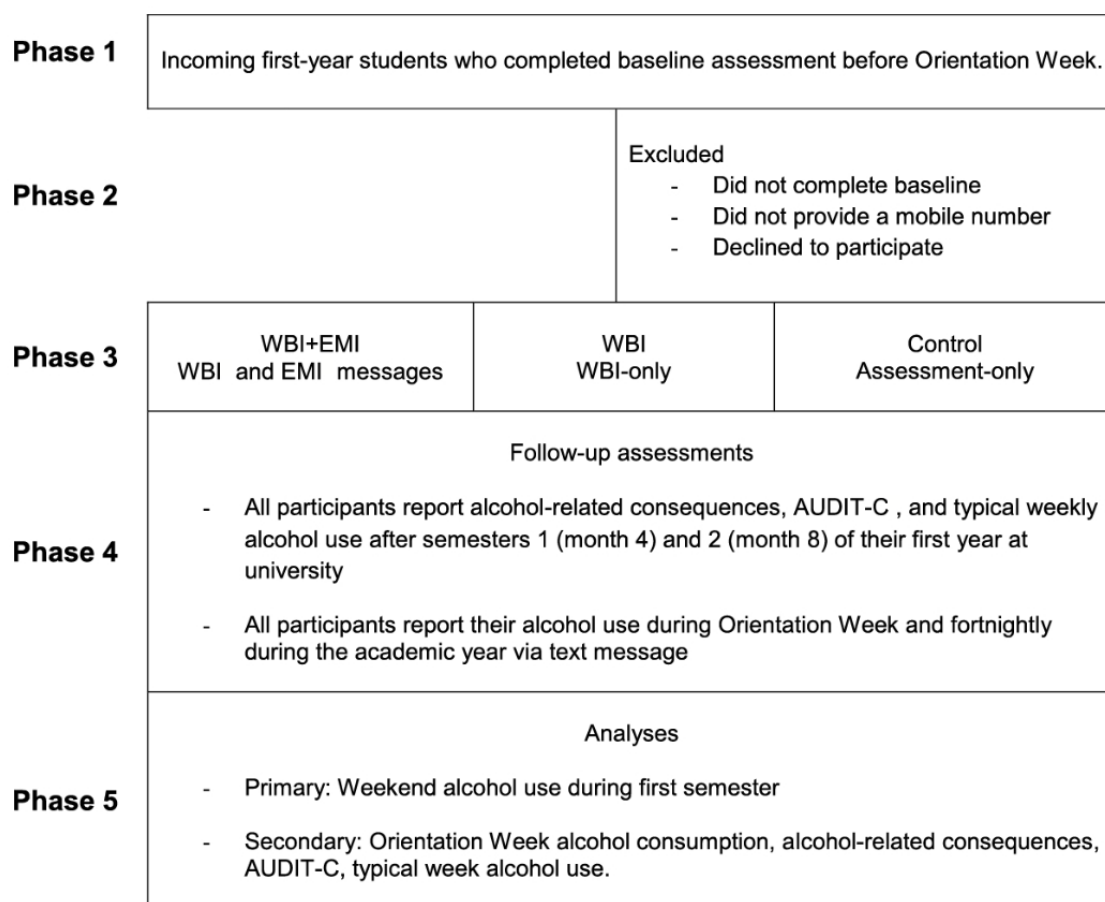
Table 1. Schedule of text messages for each group during semesters 1 and 2 of the academic year.

Condition	Semester 1							Semester 2						
	Week 1	3	5	7	9	11	13	1	3	5	7	9	11	13
Control	EMA[a]	EMA	EMA	EMA	EMA	EMA	OLS	EMA	EMA	EMA	EMA	EMA	EMA	OLS[b]
WBI[c]	EMA	EMA	EMA	EMA	EMA	EMA	OLS	EMA	EMA	EMA	EMA	EMA	EMA	OLS
WBI+EMI[d]	EMA, EMI	EMA, EMI	EMA, EMI	EMA, EMI	EMA, EMI	EMA, EMI	OLS	EMA	EMA	EMA	EMA	EMA	EMA	OLS

[a]EMA: ecological momentary assessment.

[b]OLS: online survey.

[c]WBI: Web-based intervention.

[d]EMI: ecological momentary intervention.

Orientation Week Alcohol Use

Orientation Week alcohol use [14,15] will be assessed by 2 EMAs during Orientation Week. One message will be sent on the Thursday of Orientation Week at 2:00 PM ("How many drinks did you have Mon, Tues, Wed? Send reply like this: 1,5,0") and the second will be sent on Sunday at 2:00 PM ("How many drinks did you have Thurs, Fri, Sat? Send reply like this: 1,5,0"). This procedure has been used in prior studies with good compliance (75% completed both reports) [13,14].

Negative Alcohol-Related Consequences

The number of negative alcohol-related consequences [42] experienced will be assessed by the Brief Young Adult Alcohol

Consequences Questionnaire (B-YAACQ). The B-YAACQ is composed of a list of 24 alcohol consequences, and participants simply answer yes or no as to whether they have experienced each consequence in the past 3 months. The B-YAACQ will be administered at baseline and after semesters 1 and 2 (~4 and ~8 months).

Audit-C

The AUDIT-C [43] is composed of 3 questions and provides a brief and effective screening tool for identifying likely alcohol use disorders [43]. The AUDIT-C will be administered at baseline and after semesters 1 and 2 (~4 and ~8 months).

Typical Week Alcohol Use

Number of drinks consumed during a typical week will be measured retrospectively using a modified version of a timeline follow-back procedure [44]. Participants will be asked to "Think of a typical week in the last 3 months for you. Think of what you did, where you lived, what your weekly activities were. Try to accurately remember how much alcohol you typically drank." Typical week drinking will be measured at baseline and after semesters 1 and 2 (~4 and ~8 months).

Intervention Components

WBI

The WBI will provide personalized normative feedback based on the amount of alcohol participant's report consuming during a typical week. The feedback will be specific to the University of Otago, participant's gender, and their year at university. These specific norms will be derived from the Daily Life Study, a large study that surveyed around 2000 full-time students from the University of Otago (~10% of the university population) [31,45]. The feedback includes tailored graphics and text information regarding (1) the number of drinks consumed in the past week compared with a typical first-year student of the same gender, (2) the financial cost of drinking, (3) the number of calories consumed, and (4) the number of negative alcohol-related consequences experienced in the past 3 months compared with a first-year student of the same gender. Participants will also receive feedback on their AUDIT score, feedback on their heaviest drinking session (estimated peak Blood Alcohol Content and the effects of consuming alcohol at that level), and suggest protective behavioral strategies.

EMI

The EMI consists of text messages delivered during Orientation Week and fortnightly throughout the first semester. Content includes information about protective behavioral strategies, the social consequences of drinking, and campus-based social norms. The Orientation Week messages will be sent on the nights during Orientation Week historically associated with the most drinking (ie, the first-year toga party, on nights with music

concerts, and the Saturday of Orientation Week). The specific content and timing of the messages are based on feedback from surveys [38], focus groups [15], and in-situ interviews with students outside Orientation Week events [18]. On days during Orientation Week with social events, participants will receive 1 message at 2:00 PM reminding them of a protective behavioral strategy mentioned in the WBI (eg, "Toga party tonight! If you are planning to have a few drinks, remember to eat. Food=energy! Eating is not cheating"). They will then receive 1 message timed to when they start drinking at 7:00 PM reminding them of the social consequences of alcohol (eg, "Remember, don't be a dick! Your drinking can affect your mates"; Table 2 contains the complete list of Orientation Week EMIs).

During the academic year, students will receive a fortnightly social norm message tailored to their gender (eg, "Hope you had a great OWeek! The typical female scarfie drinks no more than 6 drinks per week. OWeek is a one off, now the year begins"; see complete list of text messages in Table 3).

Randomization

Participants will be randomized into the WBI+EMI, WBI-only, or assessment-only groups. Participants who agree to take part after the initial survey will be allocated with a number (1-6) using a random number generator. Randomization is fully computerized and, therefore, is not possible to subvert.

Analytical Plan

Data Treatment

Given that our study aims to demonstrate that a combined WBI+EMI is more effective than a WBI-only and assessment-only condition, it will be categorized as a "superiority trial." Results will be presented using both the intention-to-treat principle (ie, all participants who were assigned to a condition) and complete cases (ie, participants who completed every report) [46]. The missing data for intention-to-treat analyses will be dealt with using multiple imputation.

Table 2. Complete list of ecological momentary intervention text messages during Orientation Week.

#	Time	Text	Type
1.	Wed 2:00 PM	"Toga party tonight! If you are planning to have a few drinks, remember to eat. Food=energy! Eating is not cheating."	PBS[a]
2.	Wed 6:45 PM	"These could be your friends for the year. Make sure your drinking doesn't ruin everyone's night."	SC[b]
3.	Thur 2:00 PM	"Concert tonight! Remember to smash water when drinking. Subbing water while you drink will decrease hangover symptoms. OWeek is a loong week"	PBS
4.	Thur 6:45 PM	"On it? Remember to look after your friends if you are drinking!"	SC
5.	Fri 2:00 PM	"Rugby tonight! You've made it this far. If you're drinking tonight, set a limit that works and stick to it!"	PBS
6.	Fri 6:45 PM	"Think about your friends if you are drinking. Don't be the story everyone tells tomorrow."	SC
7.	Sat 2:00 PM	"OWeek Saturday! If you're having a wet one tonight, drink slowly. Alc can hit you like a ton of bricks!"	PBS
8.	Sat 6:45 PM	"Remember, don't be a dick! Your drinking can affect your mates."	SC

[a]PBS: protective behavioral strategy.

[b]SC: social consequence.

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Table 3. Complete list of ecological momentary intervention text messages during semester 1.

Week	Text (men)	Text (women)
1	"Hope you had a great OWeek! The typical male scarfie drinks no more than 11 drinks per week. OWeek is a one off, but now the year begins!"	"Hope you had a great OWeek! The typical female scarfie drinks no more than 6 drinks per week. OWeek is a one off, now the year begins!"
3	"Drinks can set you back! The average scarfie male drinks about 11 drinks per week, that is $1144-5720 a year, OR 2-10 round trips to Raro!"	"Drinks can set you back! The average scarfie female drinks about 6 drinks a week, that is $624-3120 a year, OR 1-5 round trips to Raro!"
5	"Remember, drinks contain empty calories. The average male scarfie drinks no more than 11 drinks a week, that is about 2.3 sticks of butter"	"Remember, drinks contain empty calories. The average female scarfie drinks no more than 6 drinks a week, that is about 1.3 sticks of butter."
7	"Hope you had a good break! During this half of the semester the typical male scarfie drinks no more than 8.6 drinks a week"	"Hope you had a good break! During this half of the semester the typical female scarfie drinks no more than 4.2 drinks a week."
9	"This time of year, male scarfies typically drink no more than 8.6 drinks per week. That is about $894-4472 a year, OR 9-45 HUBs text books!"	"This time of year, female scarfies drink no more than 4.2 drinks per week. That is about $437-2184 per year, OR 4-21 HUBs text books!"
11	"This time of year, male scarfies drink no more than 8.6 drinks per week. That is about 1462 extra calories OR a cup of bacon fat!"	"This time of year, female scarfies drink no more than 4.2 drinks per week. That is about 714 extra calories OR half a cup of bacon fat"

Statistical Analysis

Given that our outcome variables of interest, with the exception of alcohol use disorders measured by AUDIT-C scale, will comprise count data (ie, number of drinks consumed and number of negative alcohol-related consequences experienced), generalized linear models (GLMs) will be employed [47]. The standard GLM, however, assumes that the observations are uncorrelated, which is certainly not the case in longitudinal designs such as this study [48,49]. Given this, extensions to the standard GLM will be employed. Briefly, generalized estimating equations (GEE) are mostly suggested for analysis of data involving 2 data levels (eg, observations clustered within individuals, or individuals clustered within groups) to investigate population-averaged changes in the outcome [50]. GLMs, however, are deemed more robust in the designs involving more than 2 levels of data (eg, observations clustered within individuals who are clustered within groups) to test individual-averaged changes in the outcome [49]. Interpreting the GEE results to make inferences about individual-specific changes over time and interpreting the GLM results to make inferences about the population's mean change over time lead to ecological and atomistic fallacies [51].

Given our interest in both population-averaged and individual-specific changes over time, and the fact that our participants will be clustered within different colleges, we will use both GEE and GLM. Specifically, GEE will be used to investigate population-averaged changes in the primary and secondary outcomes as a result of time, type of intervention, and their interaction. To deal with the potential effect of participants nested in different residential colleges, unit dummies (ie, 1 dummy for each college except for a reference college) will be added as covariates to account for any heterogeneity between the colleges.

To investigate individual-specific changes in outcomes we will use GLM. The use of GLM allows further investigation of the residential college-specific changes in outcomes. In addition to the fixed effects of time, type of intervention, and their interaction, we will add random effects for individuals and for

colleges. The addition of random effects for residential colleges is justified by our prior studies showing that different students from residential colleges have different drinking habits [15].

Prior research also suggests that alcohol interventions have different impacts on individuals with, for instance, different average alcohol consumption levels [15]. Information regarding the potential existence and the number of such unobserved, yet homogenous, subpopulations within the data, however, can only be obtained using post hoc analysis techniques such as growth mixture modeling (GMM). GMM provides the framework necessary for identifying multiple unobserved subpopulations, examining each unobserved subpopulation's trajectory over time and in comparison with the other unobserved subpopulations [52]. For this study, GMM will shed light on possible differences in the effectiveness of the proposed intervention for students with various drinking habits.

Across analyses, baseline characteristics will be controlled for as we expect that gender and baseline alcohol consumption might influence the effectiveness of the intervention [9].

Sample Size Calculations

A series of power analyses were performed to estimate the sample size required to detect a small interaction effect between time and type of intervention (the estimated effect size=-0.1) on student's number of weekend drinks. The target was at least 80% power. Given that we are only interested in 2 estimated effects (ie, the main effect intervention and the interaction effect between time and intervention), a Bonferroni-adjusted family wise alpha of .025 was assumed for the power analysis [53]. All the analyses were conducted using R (R Foundation for Statistical Computing) and were based on a dataset obtained from a previous pilot experimental study [15].

Taking a conservative approach, we first estimated the sample size for a GEE with the main effects of time, type of intervention (ie, treatment), their interaction, and the main effects of gender and baseline alcohol consumption (ie, baseline). To this end, we used the GEE and long-power packages to estimate the minimum sample size required [54,55]. The results of analysis

suggested a sample size of 527 to 553 students based on assuming an unstructured or an exchangeable correlation matrix.

Next, based on Monte Carlo simulations and using the estimated sample size required for the GEE analysis (ie, 553), we evaluated the power of performing GLM analysis. All the analyses were performed using the lme4 and simr packages in R [56,57]. First, we fitted a 2-level mixed effect model with the fixed effects of time, type of intervention (ie, treatment), their interaction, gender and baseline alcohol consumption (ie, baseline), and the random effect of student. The simulation results revealed a statistical power 97%, with 95% CI=91.48-99.38. Moreover, for a 3-level mixed effect model with the fixed effects of time, type of intervention (ie, treatment), their interaction, gender and baseline alcohol consumption (ie, baseline), and the random effects of student and college, the results of simulation showed a statistical power 98%, with 95% CI=92.66-99.76. Hence, our analysis suggested that a sample of 553 students would provide sufficient power for either 2- or 3-level mixed effect models.

Finally, considering an additional 25% dropout rate [15], we came up with a final target sample size of 692 students (the pilot dataset and the details of power analyses, eg, R codes, results, and power curve plots are available upon request from the first or last author).

Discussion

Summary

As noted above, the transition to university is associated with an increase in alcohol consumption [9]. One factor that contributes to this increase is Orientation Week [14-16]. Indeed, research on Orientation Week suggests that new students double their drinking relative to a typical week before university [14]

and experience 5 times as many negative alcohol-related consequences [17]. With the aim of curbing these increases in consumption and harm, this protocol outlines a large-scale long-term RCT to test a WBI+EMI intervention.

Limitations

This study is not without limitations. First, although the WBI provides individually tailored feedback, the content of the EMI messages is only tailored to the student's gender. It is, however, important to remember that EMI messages were developed based on feedback from surveys [38], focus groups [15], and in-situ interviews with students outside Orientation Week events [18]. A second limitation is that there is a high degree of contact required for the assessment-only condition. It is possible that, due to regularly being asked to report how much alcohol they have consumed, participants in the assessment-only condition will reduce their levels of alcohol consumption and harm. Typically, participants in assessment-only control conditions are assessed at baseline and then at the end of the study. In this study, the assessment-condition consists of 2 assessment messages during Orientation Week and fortnightly assessment messages during the academic year (in addition to the baseline and follow-up assessments). The benefit of this approach is that we can compare the 3 arms of this RCT with a great deal of temporal precision. The limitation of this approach is that any effects observed will likely be smaller than those observed if we simply conducted a baseline assessment and long-term follow-up.

Conclusions

This study adds to a growing body of work investigating the utility of WBIs and EMIs in curbing alcohol consumption. In addition, the study will help to inform policy approaches aimed at curbing alcohol consumption and alcohol-related harm in university students.

Conflicts of Interest

None declared.

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Abbreviations

AUDIT-C: Alcohol Use Disorder Identification Test-Consumption
EMA: ecological momentary assessment
EMI: ecological momentary intervention
GEE: generalized estimating equations
GLM: generalized linear models
GMM: growth mixture modeling
OLS: online survey
PBS: protective behavioral strategy
SC: social consequence
WBI: Web-based intervention

Protocol

Optimizing Gestational Weight Gain With the Eating4Two Smartphone App: Protocol for a Randomized Controlled Trial

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Abstract

Background: Approximately 50% of women gain excessive weight in pregnancy. Optimizing gestational weight gain is important for the short- and long-term health of the childbearing woman and her baby. Despite this, there is no recommendation for routine weighing in pregnancy, and weight is a topic that many maternity care providers avoid. Resource-intensive interventions have mainly targeted overweight and obese women with variable results. Few studies have examined the way that socioeconomic status might influence the effectiveness or acceptability of an intervention to participants. Given the scale of the problem of maternal weight gain, maternity services will be unlikely to sustain resource intensive interventions; therefore, innovative strategies are required to assist women to manage weight gain in pregnancy.

Objective: The primary aim of the trial was to examine the effectiveness of the Eating4Two smartphone app in assisting women of all body mass index categories to optimize gestational weight gain. Secondary aims include comparing childbirth outcomes and satisfaction with antenatal care and examining the way that relative advantage and disadvantage might influence engagement with and acceptability of the intervention.

Methods: This randomized controlled trial will randomize 1330 women to control or intervention groups in 3 regions of different socioeconomic status. Women will be recruited from clinical and social media sites. The intervention group will be provided with access to the Eating4Two mobile phone app which provides nutrition and dietary information specifically tailored for pregnancy, advice on food serving sizes, and a graph that illustrates women's weight change in relation to the range recommended by the Institute of Medicine. Women will be encouraged to use the app to prompt conversations with their maternity care providers about weight gain in pregnancy. The control group will receive routine antenatal care.

Results: Recruitment has commenced though the recruitment rate is slower than expected. Additional funds are required to employ research assistants and promote the study in an advertising campaign.

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Conclusion: Feasibility testing highlighted the inadequacy of the original recruitment strategy and the need to provide the app in both major platforms (Android and iOS). Smartphone technologies may offer an effective alternative to resource intensive strategies for assisting women to optimize weight gain in pregnancy.

Introduction

Background

Obesity is one of the most significant health issues of our time. Regardless of prepregnancy body mass index (BMI), the amount of weight gained during pregnancy (gestational weight gain, GWG) has the potential to impact the health and well-being of the childbearing woman and her baby in the short, medium, and long term. Women who gain excessive weight in pregnancy are more likely to retain weight in the short, medium and long term, progressing from normal weight to obese over their childbearing years. There is a critical need to reduce the burden of maternal obesity and excessive GWG with programs that are effective, accessible, and scalable for delivery at a population level, and to understand how socioeconomic factors impact GWG and uptake of interventions. This research proposal addresses these 2 key issues by examining the efficacy of the Eating4Two smartphone app in a population of pregnant women of all BMI categories and varying levels of socioeconomic advantage and disadvantage.

Optimizing GWG is important to the short- and long-term health of the childbearing woman and her baby. Excess GWG is associated with maternal hypertensive disease, and caesarean section [1] is an independent risk factor for large for gestational age infants [2], and may have long-term consequences for the neonate. Independent of maternal BMI, excessive GWG is associated with childhood adiposity at birth [3] and 3 [4] and 5 years of age [5]. These data suggest that careful management of gestational weight gain is as important for the offspring of underweight and normal weight women as it is for the overweight and obese.

Excessive gestational weight gain may also influence maternal health beyond the duration of the pregnancy. A systematic review and meta-analysis of studies examining maternal weight gain, neonatal outcomes, and maternal weight retention found that women who experienced excess GWG were more likely to retain excess weight in the short, medium, and long term [6]. This has implications for subsequent pregnancy outcomes. Our previous work has shown that multiparous women who had an interpregnancy increase of 3 BMI units or more had significantly increased odds of low 5-min Apgar score, gestational diabetes, and hypertensive disorders in the subsequent pregnancy in adjusted analyses, independent of previous BMI [7]. There are also consequences for long-term chronic disease risk [8]. Maternal and neonatal outcomes are optimized when women begin their pregnancy at a healthy weight and maintain a healthy weight throughout pregnancy. Maternal overweight and obesity is associated with increased risks of gestational diabetes, hypertension, induction of labor, stillbirth, preterm birth, major congenital malformations, large babies, shoulder dystocia, caesarean section, wound infections, and postpartum hemorrhage [9-13]. These risks increase with increasing maternal BMI [10]. Prepregnancy maternal weight also has long-term consequences for the neonate. Babies born to women who are overweight or obese have a higher likelihood of childhood overweight and obesity [14]. Although the mechanism underpinning this intergenerational effect is not yet clear, some researchers (though not consistently) have identified epigenetic modifications in offspring of under- and over-nourished women [15]. Intergenerational patterns of obesity and the potential for epigenetic effects in the offspring of overweight and obese women, means that childbearing women are a critical target population for interventions aimed at addressing obesity in the general population.

Table 1 shows the gestational weight gain recommendations of the Institute of Medicine (IOM) for women of varying BMI categories [16]. Although these recommendations are officially endorsed in Australia by the Royal Australian and New Zealand College of Obstetricians and Gynecologists, the recommendations for weight gain in pregnancy they are rarely referred to in practice. The prevalence of GWG in excess of the IOM guidelines in developed countries is approximately 50% [16]. Of concern is that younger and nulliparous women have a greater likelihood of gaining excess weight during pregnancy. Pregnancy is a significant life event for women and it is a time that many women are motivated to focus on their health. Furthermore, pregnancy offers an opportunity to positively impact the short- and longer-term health of 2 individuals with a single intervention.

Table 1. Institute of Medicine gestational weight gain recommendations.

Prepregnancy BMI[a] (kg/m^2)	Recommended weight gain (kg)
<18.5	12.5-18
18.5-24.9	11.5-16
25-29.9	7-11.5
>30	5-9

[a]BMI: body mass index.

Various resource-intensive interventions have been developed to assist overweight and obese women to manage their weight gain in pregnancy with varied success. These include one-to-one dietary counseling and targeted exercise programs [17]. The LIMIT trial, for example [18], randomized over 2000 overweight and obese women to a control condition or antenatal dietary and lifestyle intervention and found no differences in maternal pregnancy and birth outcomes, GWG or risk of large-for-gestational-age babies between groups. Babies born to mothers in the intervention group, however, were significantly less likely to have a birth weight greater than 4000 g.

The UPBEAT trial in the United Kingdom [19] randomized 1555 obese women to control or to an intervention that included coaching by a health trainer at enrolment and a further 8 individual or group sessions over the pregnancy. This study identified no differences between control and intervention groups in the primary outcomes of gestational diabetes and large-for-gestational-age infants; however, there was a small but significant difference in total GWG with women in the intervention group gaining 0.55 kg less than those in the control group. A recent systematic review with economic analysis of diet and lifestyle interventions aiming to assist with GWG found no evidence that interventions in pregnancy are cost effective or clinically effective [20]. Given the magnitude of the problem of maternal weight gain in the population and the already stretched resources of maternity services, it is unlikely that such resource-intensive interventions will be sustainable even if they do prove to be effective. New and innovative ways of addressing GWG in a sustainable way that can benefit all pregnant women, not just those who are overweight or obese, are a high priority.

Development of an App to Optimize Gestational Weight Gain

This led us to the development of a mobile phone app: Eating4Two (the app) [21] (see Figure 1 for app icon). Experts in nutrition and dietetics, public health, midwifery, and obstetrics contributed to its development drawing on the information-motivation-behavioral skills approach to behavior change [22]. Childbearing women were involved in various stages of the development. The welcome screen reminds users that the aim of the app is to augment rather than replace maternity care (see Figure 2 [left] for welcome screen).

The app (developed originally in the Android platform and now available in Android and iOS) is aimed at all pregnant women

(in every BMI range), providing them with information on diet and nutrition in pregnancy drawing on the National Health and Medical Research Council's Nutrient Reference Values for Australia and New Zealand [23]. The app contains a library of information (see Figure 2, right) that includes the following tabs: nutrients (describing important nutrients required for pregnancy and foods that contain them), foods (describing the main food groups and recommended serving sizes; see, eg, Figure 3, left), meals, (providing sample meal plans), symptoms (advice on how to manage common pregnancy symptoms, eg, heartburn), behaviors (providing advice on lifestyle behaviors including use of alcohol and managing cravings), and references.

BMI is calculated based on self-reported prepregnancy weight and height, and based on this information, a tailored gestational weight gain range is calculated. Women are encouraged to plot their weight on a graph weekly (which provides real time feedback on their GWG) based on the IOM recommendations (see Figure 3 [right] for weight tracker).

Self-monitoring of weight has been identified as an effective strategy in weight loss interventions [24]. Women are provided with instruction on how to weigh themselves and are asked to focus on trends rather than individual results. When weight gain is above or below the recommended range, women are prompted to discuss the issue with their maternity caregiver so that individualized advice can be provided. The app is intended to augment maternity care and to empower pregnant women to manage their GWG. In addition, push notifications are delivered based on the individual's gestation, providing information on the size of the fetus and relevant nutritional information. No prompts or reminders are used to encourage use of the app.

Mobile phones have the potential for scalability of interventions, given their ubiquitous distribution in Australia. The Australian Bureau of Statistics reports that as of June 2017, there were 26.3 million mobile phone subscribers with access to the Internet in Australia [25]. Smartphone ownership in the 25-34 years and 35-44 years age groups (the main childbearing years) in Australia is 85% and 81%, respectively. In the 6 months leading up to May 2013, 76% and 66% of people in these age ranges had downloaded a mobile phone app [26]. A small qualitative study focusing on pregnant women in South Australia (*n*=35) found that all participants had access to a mobile phone and that the majority of these were smartphones [27]. Moreover, 40% of these participants reported having used at least one pregnancy-related mobile phone app.

Figure 1. Eating4Two App icon.
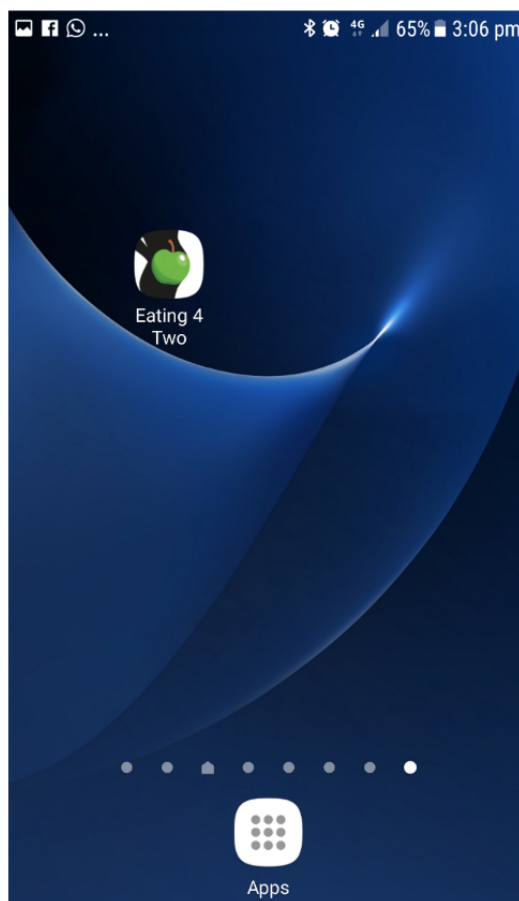
Figure 2. Eating4Two welcome screen (left) and library screenshot (right).
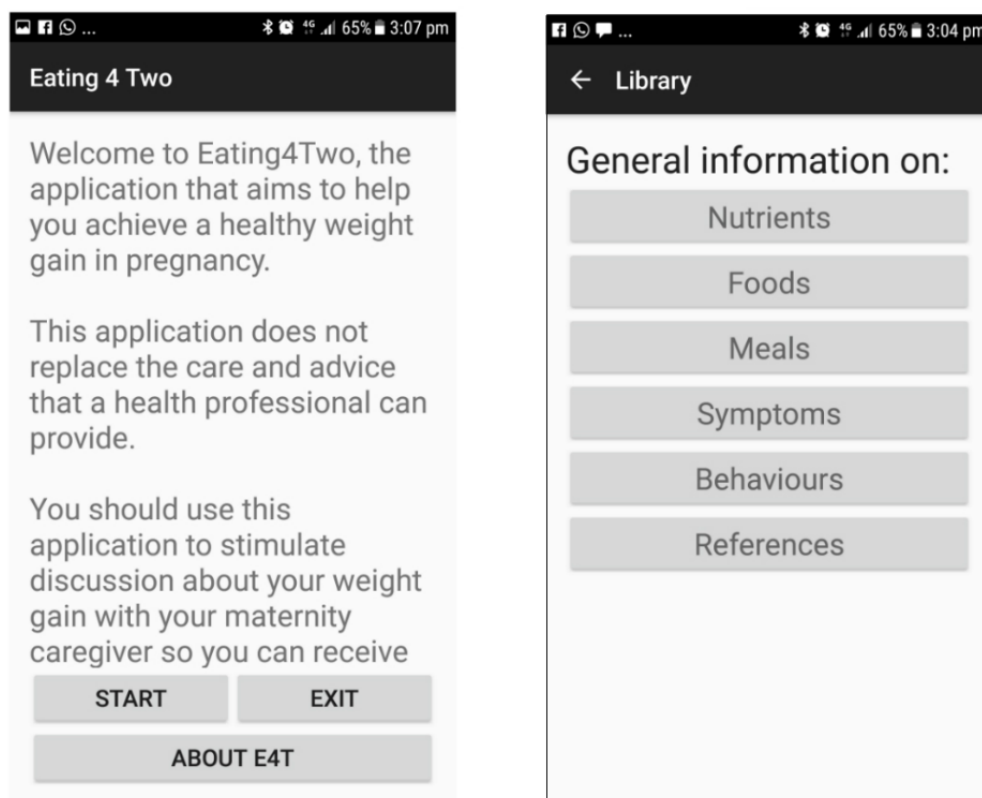
Figure 3. Eating4Two recommended serving size fruit (example; left) and weight tracker (right).
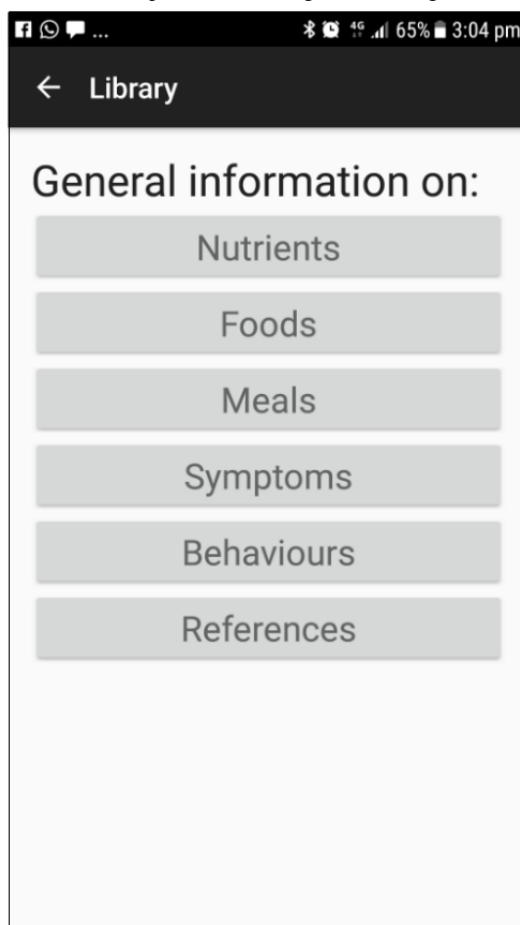
Despite the rapid increase in the number of apps and other mHealth interventions available in the field of maternal and newborn health [28], there is a paucity of robust studies that objectively measure clinical outcomes for the mother or newborn [29-31]. Much of the research has focused on middle- and low-income countries [30,31] due to the high need for interventions to improve poor perinatal outcomes in these low-resource settings and rapidly improving mobile technology infrastructure. Studies have shown that mHealth interventions (short message service, SMS, support) has improved service utilization and vaccinations rates [29], reduced risk of perinatal death, and improved breastfeeding rates [30]. Focusing more globally, Chen's recent [28] systematic review highlights the rapid increase in studies focusing on mHealth interventions, noting that interventions in resource-poor countries tended to focus on infections disease and essential care, whereas those from developed countries focused on noncommunicable diseases such as asthma or diabetes.

Despite the increase in studies, Chen et al concur with others when they comment on the poor quality of many studies in this area.

Mobile phone apps are developed by individuals, groups, and organizations representing public and private interests, and vary greatly in their quality. Health care professionals are also increasingly turning to mobile phone apps to deliver health care interventions, particularly in the area of preventative health [32]. A systematic review examining new communication technologies and their potential to support lifestyle interventions during pregnancy [33] identified 7 completed and ongoing studies using a range of technologies from websites (3), video (1), phone (1), and smartphone apps (2). The latter group included one pilot study focusing on physical activity and pregnancy [34] and one ongoing study focusing on GWG in the United States [35]. Targeting overweight and obese women, this 3-arm randomized control trial includes the following: standard care (physician directed), regular meetings with a weight management counselor during pregnancy (SmartMoms-clinic), and 2 individual meetings with a weight management counselor, followed by weekly messages via smartphone from the counselor (SmartMoms-phone).

Western Australian researchers have developed a Web-based resource, *Healthy You, Healthy Baby* [36]. The website and app are aimed at providing women with information on a range of topics including nutrition, physical activity, weight, emotions, social life, and sleep patterns. The researchers estimate that the website and app have been accessed by approximately 7% of all pregnant women in Western Australia and report that the section on weight was the most highly accessed. Although the effectiveness of this intervention is yet to be established by a research trial, the authors conclude that the strategy is a cost-effective way of providing women with accurate information about weight and other relevant perinatal issues [36].

Interventions that target individual behavior (rather than structural change) have been criticized for increasing the socioeconomic gradient of obesity [37]. The burden of overweight and obesity is felt most significantly in populations from lower *socioeconomic positions*. As those with fewer resources are less able to make the changes required of behavioral interventions, these types of interventions are hypothesized to impact most positively on those who can (those in the highest socioeconomic position). There is some support for this hypothesis coming from a study on an Internet-based intervention for limiting GWG in the United States [38]. The researchers measured engagement with the Web-based interventions according to demographic variables. Although they were generally encouraged by the engagement of all groups with the intervention, they found that white, higher income women were more consistently engaged with the Web-based resource than minority and low-income women. Again, the weight tracker was the most highly accessed resource within the intervention.

Despite the ubiquity of mobile phones in Australia and the growing use of this technology by researchers in health care more broadly, there is a paucity of research testing interventions with this technology in pregnancy. Intensive interventions for GWG, and overweight and obesity in maternity, are beyond the capacity of existing services. New and innovation solutions are required. The intervention developed is an innovative and potentially scalable solution that aims to empower women to take control of the issue in partnership with their maternity care provider. Importantly, the study will also examine the implementation of the intervention in areas with a different Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD).

Study Focus and Aims

Using a randomized control design with qualitative components, the RCT study will primarily examine the effectiveness of the Eating4Two smartphone app in assisting pregnant women to limit GWG to within the range recommended by the IOM. In addition, it will examine the acceptability of the intervention and engagement with the app for women with varying indices of relative socioeconomic advantage and disadvantage (IRSAD). The secondary aims of the study include examining clinical outcomes and satisfaction with perinatal care for women in both groups and drawing on qualitative data, comparing the experiences and challenges of women from areas with varying IRSAD.

Methods

Study Design and Overview

This study is an unblinded, 2-armed randomized control trial that will test the primary hypothesis that a greater proportion of women in the intervention group compared with the control group will limit GWG within the range recommended by the IOM. We will randomize 1330 pregnant women to the control and intervention groups. Those in the control group will receive usual antenatal care, and those in the intervention group will receive usual care augmented with the smartphone app. Participants allocated to the intervention group are prompted

by the smartphone app to discuss weight changes with their maternity or health care provider. The researcher responsible for analyzing the data will be blind to group allocation.

Settings

The proposed study will be implemented in 3 geographic regions. Region 1 is the Australian Capital Territory (ACT) and will include women attending the Centenary Hospital for Women and Children (a tertiary-level hospital) and Calvary Hospital (a sub-acute facility). These hospitals facilitate over 5000 births per annum [39]. Region 2 is the Hunter New England region of NSW, Australia, and will include women attending the John Hunter (a tertiary-level hospital) and Maitland (a sub-acute facility) hospitals. These hospitals facilitate approximately 5700 births per annum [40]. Region 3 is Port Macquarie-Hastings and includes women attending Port Macquarie Base Hospital (a sub-acute facility) that facilitates approximately 2000 births per annum.

The index of relative socioeconomic advantage and disadvantage, developed by the Australian Bureau of Statistics draws on census data to describe the economic and social conditions of people and households in a geographical area, the smallest area being a Statistical Area 1 (SA1), which includes approximately 400 people. A low score reflects greater disadvantage and a high score greater advantage [41]. The ACT as a whole, has an IRSAD decile ranking of 10 though individual suburbs range in decile rankings from 7-10. The Newcastle local government area (in which the John Hunter and Maitland Hospitals are situated) has a ranking of 7 and draws on areas with rankings that range from 3 to 7; Port Macquarie has a ranking of 5, drawing on areas with rankings ranging from 1 to 10.

In all settings, private obstetricians provide maternity care with antenatal appointments occurring in their private rooms. Their clientele will give birth in either in public or private hospitals. Public maternity care is provided by many health practitioners (including midwives, general practitioners, obstetricians or obstetricians in training) in community and hospital settings in one of the 2 models. First, women choosing a *shared care* model will have some antenatal appointments with general practitioners in their clinic rooms and some in the hospital-based antenatal clinic where they will be seen by employed obstetricians, obstetricians in training or midwives. Second, women choosing a public *midwifery led* model of care will primarily see midwives throughout the antenatal period in the antenatal clinic, birth center, and sometimes community settings. Both groups will be eligible to participate in the study. Labor and birth care is provided in the birth units of the participating hospitals.

Participants

Participants will be pregnant women who plan to give birth in 1 of the 5 participating hospitals. Inclusion criteria for participants are as follows: (1) 18 years of age or older, (2) ability to provide informed consent, (3) fluent in written and oral English language, (4) less than 15 weeks gestation at recruitment, (5) personal ownership of a smartphone, (6) access to weighing scales, and (7) a valid email address and access to Internet. Potential participants will be excluded if they are

planning to give birth in a nonparticipating hospital; have a multiple pregnancy, Type 1 or 2 diabetes before pregnancy, and barriers to accessing or using a smartphone for the duration of the trial; or their health care provider considers use of the app or GWG in accordance with IOM recommendations detrimental to the potential participant.

Recruitment and Randomization

Recruitment will be via social media and health professionals providing antenatal care or childbirth education. Social media will publish the research aims and eligibility criteria and invite potential participants to contact the research assistant who will provide more information and a research information pack. Health professionals will introduce the study to potential participants and provide those interested and eligible with a research information pack. They will also collect contact details of those expressing an interest (for follow up by the research assistant). The research information pack contains a concise lay description of the study, contact details of the researchers, a hard copy questionnaire to establish baseline demographic details, consent form, and reply-paid envelope. The research assistant will contact all those provided with an information pack to discuss potential participation and answer any questions they may have. Those who agree to participate will complete the consent form and questionnaire and return these to the research coordinator in the reply-paid envelope provided. The research coordinator will record the date of receipt.

The research coordinator will randomize participants on receipt of the signed consent form. Participants will be randomized using a 1:1 ratio in balanced blocks and stratified by BMI and geographical setting. Allocation concealment will be assured through the use of a remote Web-based allocation service.

Control and Intervention

The control group will receive usual antenatal maternity care with the addition of a written nutrition and weight gain resource: the booklet "Good nutrition in pregnancy," published by the ACT Government. Usual care for women includes attendance at antenatal appointments in accordance with the following gestation schedule: 12-14 weeks (booking visit), 16, 20, 26, 30, 33, 36, 38, 40, and 41 weeks. Women choosing shared care usually alternate visits with their general practitioner and hospital clinic. Although women's BMI is calculated at their first hospital-booking visit, weighing is not routinely attended at subsequent antenatal clinic appointments or at labor commencement. Advice on weight gain is ad hoc, and dietary advice is focused on food safety in pregnancy. Women with a BMI over 35 kg/m^2 are referred to a community dietitian. Some amendment to usual care will be required to weigh women at 38 weeks and at commencement of labor.

The intervention group will receive usual care as outlined above and will also be provided access to the Eating4Two smartphone app at no cost. The app, password protected, will be able to be downloaded from App stores. The app provides dietary information appropriate to pregnancy and advice on good nutrition (drawn from the Australian Dietary Guidelines 2017 [23]), managing common pregnancy-related symptoms (such as heart burn), and GWG. Photographs are included that demonstrate serving sizes for relevant food groups. The woman's weight is graphed against the range recommended by the IOM for their starting BMI and records this information, making it available for the researchers. When weight gain is above or below the recommended range, women are prompted to discuss the issue with their maternity caregiver so that individual advice can be provided. The app also sends regular messages to the participant (specific to their gestation) with information about their baby's growth, development and nutritional needs, motivational messages, tips on weight management and physical activity in pregnancy, and reminders to discuss weight gain with their maternity caregivers. The aim of the app is to augment usual antenatal care by providing information to women about nutrition, empowering them to monitor their GWG, and encouraging discussion of weight between women and their maternity caregivers when GWG deviates from the recommended levels.

Data Collection

The weight of all women will be established prepregnancy (self-reported), pregnancy (at enrolment in study <15 weeks gestation, self-reported), at approximately 38 weeks gestation (measured), commencement of labor (measured), and at 6 months postpartum (self-reported). The weight of women in the intervention group as recorded by the women in the app will also be available to researchers. Routinely collected clinical maternity data will be used where possible and this will be drawn from clinical records. This includes demographic data (age, parity, ethnicity and address) and behaviors including smoking and clinical outcomes. Using geo-coding, addresses of women participating in this study will be matched to the Australian Bureau of Statistics geographical data and allocated an IRSAD score. Data not collected routinely (including education and marital status) will be sought from participants (via a questionnaire), which will include participation in exercise and dietary intake established at baseline and repeated at approximately 38 weeks gestation, information about the GWG resources and advice accessed by women (38 weeks) and their rating of the app (38 weeks for intervention group only). Satisfaction with perinatal care will be assessed by questionnaire at 4-6 weeks postpartum.

The primary outcome will be GWG, specifically the proportion of women whose GWG falls within the range recommended for them by the IOM for their baseline BMI. GWG will be calculated by subtracting the woman's first recorded pregnancy weight from her recorded weight in labor. Secondary outcomes including pregnancy complications, labor interventions, mode of birth, and neonatal outcomes will be drawn from routinely collected maternity outcome data and will include the following data: complications arising in pregnancy including hypertension and gestational diabetes (as diagnosed by health professional), labor interventions (including induction or augmentation of labor), mode of birth (spontaneous vaginal, assisted vaginal, caesarean section), birth complications (eg, shoulder dystocia), and neonatal outcomes (including gestation, birth weight, admission to neonatal nursery, Apgar score).

Women allocated to the intervention group will be required to enter the following initial data into the Eating4Two app: height,

prepregnancy weight, and baby's due date. Thereafter, they will be requested to enter their weight on a weekly basis. Data transferred to the researchers directly from the app include height, prepregnancy weight, baby's due date, and weekly weights. Four to six weeks after the participant's due date, they will be sent an email containing a link to a Web-based questionnaire in Qualtrics assessing quality of perinatal care. The Quality Perinatal Care Questionnaire is a 46-item instrument with 6 validated subscales originally developed in Canada and validated in an Australian population [42]. This email will also contain an invitation to participate in a focus group or individual interview. This component seeks to understand the barriers and facilitators to optimal GWG in pregnancy from a personal, social, and health care perspective, and specifically to understand how these may differ for women of different prepregnancy BMI and IRSAD (index of relative social advantage and disadvantage) groups. Those in the intervention group will also be asked specific questions about the app, which will provide additional information on the components of the App and its acceptability, functionality, engagement, and motivational capacity.

Additionally, this seeks to explore how BMI and IRSAD might impact app evaluation. Focus groups will aim for between 8 to 12 participants in each session, and intervention and control group women will attend separate groups. We will also attempt to group women living in areas with similar IRSAD scores and prepregnancy BMI categories together so that we can examine the ways in which these factors might impact issues relating to gestational weight management, engagement with maternity care providers, and engagement with the Eating4Two app(for those in intervention group). We will aim for 8 focus groups in total (64-96 participants). Individual interviews (by phone) will be offered to those who cannot attend focus groups.

It can be difficult for new mothers to attend scheduled focus groups, and individual phone interviews offer greater flexibility. We will aim for a total of 20 individual interviews balanced between intervention and control groups and sites. All focus groups and interviews will be audio recorded and transcribed verbatim.

Data Analysis

Primary analysis will be conducted with the researcher responsible for analysis blinded to group allocation. An intention-to-treat analysis will be conducted including withdrawals and losses to follow-up. Although even distribution of baseline characteristics between the intervention and the control groups is expected due to randomization, this will be further assessed by Chi-squared test and Student t-test for categorical and continuous variables, respectively. Descriptive statistics for all outcome variables will be calculated before statistical analysis. Continuous outcome variables will be evaluated for normality and transformations will be applied as necessary. Regression analysis with adjustments for confounding variables (prepregnancy BMI, smoking, IRSAD score, parity, age) will be used to evaluate the primary outcome and relative risk, and its 95% CIs will be calculated. Significance will be set at .05. The multiple imputation method will be used to generate possible values for missing values. This is considered

gold standard for dealing with missing data. Data will be analyzed in IBM SPSS Statistics).

Qualitative data analysis will firstly follow a simple descriptive approach using NVIVO 11 software (QRS International). Qualitative descriptive analysis is a low-inference analysis that uses an inductive approach to develop descriptive themes. All transcripts will be coded by first attaching a descriptive label to each meaning unit (a sentence or group of sentences conveying a message or concept relevant to the study); first level. Descriptive labels will be examined and grouped with other labels conveying a similar idea to create descriptive themes; second level. Data will be analyzed within groupings (BMI and IRSAD) and then compared across groups; third level. This will be attended by 2 researchers independently (first level) and then collaboratively on the second and third levels of analyses.

Sample Size

This trial is designed to detect a clinically significant increase in the proportion of women who have a gestational weight gain within the current IOM recommendations from 36% to 42%. A recent prospective study in Australia with 664 participants (of all BMI categories) found that 36% of the cohort gained within the range recommended by the IOM [43]. This is greater than the proportion found in the LIMIT trial (33%), though this trial included only overweight and obese women [18] who are known to be more at risk of excessive weight gain. A total sample size of 1156 (578 in each group) will allow detection of statistical significance with 80% power and two-sided 5% significance level [44].

The follow-up period is short in studies using GWG as the primary outcome, given the end point is birth. However, there is wide variation in reported drop-out and loss to follow-up rates, which range from 3% to 20% [18,45-47]. These are composed largely of women experiencing miscarriage, fetal loss, and moving out of area. Taking a conservative approach, we have allowed for a 15% drop-out rate, which gives a total recruitment target of 1330 women.

Ethics

The study received multi-site ethics approval from the ACT Health Human Research Ethics Committee (ETH.5.16.064). All potential participants will be supported to make an informed choice regarding joining the study and will be required to sign a consent form before enrolment. Consent includes consent to access the individual's data from clinical databases at each participating hospital. Individual data will not be reported and participant confidentiality will be protected.

Trial Status

Due to resource limitations, the Eating4Two mobile phone app was originally developed in the Android platform only. Over 4 months from October 2014 to February 2015, we attempted to recruit 80 women at one site only to determine study feasibility. Eligibility for the study included ownership of an android smartphone. Exclusion criteria included gestation greater than 18 weeks, multiple pregnancy, and preexisting clinical conditions including diabetes. A research assistant approached

women waiting for antenatal appointments at the busiest antenatal clinics in the hospital and in the community, 2 days per week. The recruitment strategy aimed to avoid burdening

already busy clinicians with the additional task of recruiting to the study.

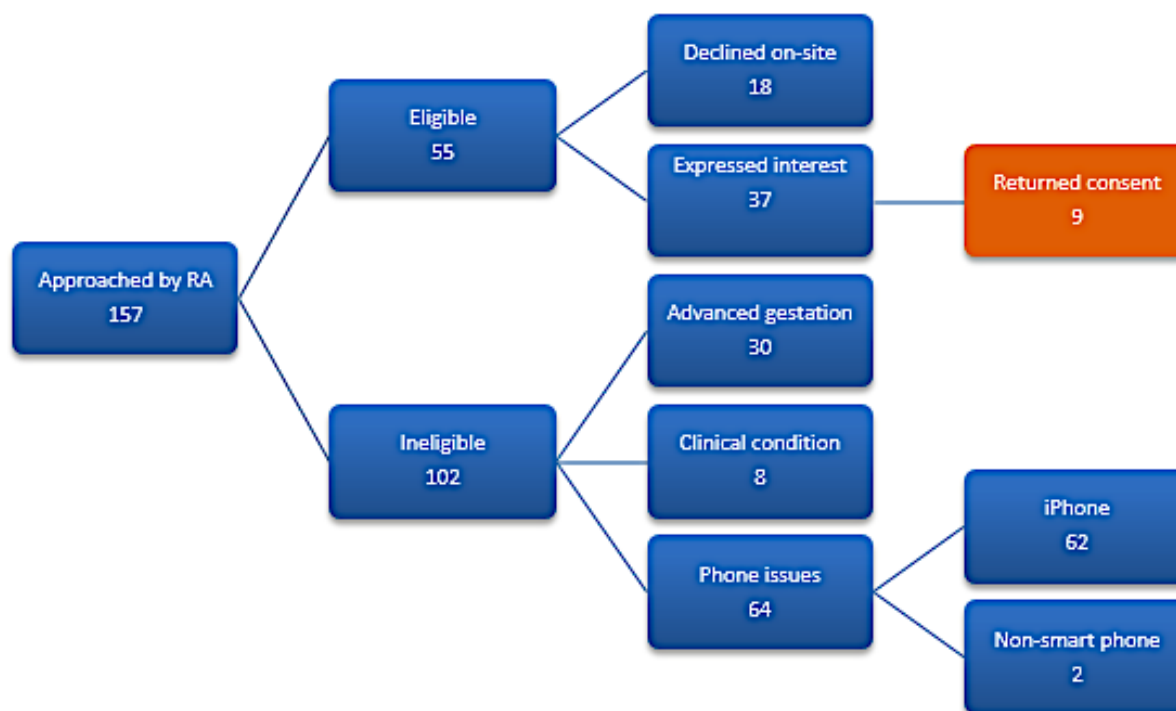**Figure 4.** Feasibility study recruitment results. RA: Research Assistant.

Figure 4 illustrates the results of the recruitment. In this period, 157 women were approached and only 9 women were successfully recruited to the study. The majority of women who were ineligible were so because they owned an iPhone rather than Android. Almost 30% were ineligible due to stage of gestation. Over 75% of eligible women who expressed an interest and were provided with a research pack failed to return a signed consent form and baseline questionnaire and thus enroll into the study.

Results

The project is currently recruiting though with a rate of 100 recruitments in approximately 12 months, recruitment is slower than expected. Additional funds are being sought to enhance recruitment through the employment of additional research assistants and a comprehensive advertising strategy.

Discussion

Principal Findings

This protocol aims to determine whether the use of the smartphone app Eating4Two is effective in assisting women to optimize GWG and improve birth outcomes. The intervention takes advantage of smartphone technology, addresses the problem of the limited health service resources available to meet an expanding area of need, and focuses on empowering women to manage their weight in partnership with their maternity care provider. In addition, it addressed the question of whether the intervention impacts differently women with varying levels of relative socioeconomic advantage and disadvantage.

Our feasibility study clearly identified problems in both the recruitment strategy and in the app platform. Although iOS (iPhones) is more popular with younger populations [48], both the Android and iOS providers dominate the field in Australia, and providing the app in both platforms will greatly increase study eligibility.

The recruitment strategy was also revised to involve a range of maternity care service providers including general practitioners, private obstetricians, employed obstetricians, and midwives. Most women visit their general practitioner to confirm their pregnancy, and this makes this group particularly important to ensure that women are recruited early to resolve the other main issue compromising eligibility of advanced gestation. Relying on clinicians can be a risky recruitment strategy as they are often busy and prioritize clinical care. There are, however, a number of strategies that will be employed to enhance the strategy including early engagement; study logo; and regular communication through a study newsletter, eg, acknowledging participation (with merit letters or certificates for example) and showing appreciation [49].

Digital Preservation

During the trial period, the app will only be available to research participants only, though source coding and App content have been preserved. Researchers interested in replicating this trial will be invited to contact the researchers directly. Health care interventions such as the Eating4Two app must be evaluated carefully to ensure no harm is brought to the pregnant woman or fetus.

Limitations

The study relies on self-reported height and weight to establish the BMI of participants in the intervention group. Maternity care providers usually calculate BMI at the first antenatal booking visit, and participants can correct these data within the application if necessary. Nonetheless, it is reliant on the accuracy of the participant's entry. Total weight gain is established by subtracting the woman's first recorded pregnancy weight from her recorded weight in labor, and we will be unable to vouch for the accuracy of the scales used in various antenatal and labor and birth settings. The quality of the scales used and the procedures for maintaining and calibrating them may vary. Although this may affect the results of the study, it is important to test methods that will be used in translating the intervention to service delivery if successful. Finally, this study does not include any follow-up of women to assess their longer-term weight change post birth.

Conclusions

Many women gain excessive weight during pregnancy, and this causes problems for the index pregnancy and contributes to the burden of overweight and obesity in society, as excessive gestational weight is often retained postpregnancy. To date, research has focused on intensive interventions that are costly for health services and are unlikely to be sustainable. Few studies have examined the way that women from varying socioeconomic positions might receive interventions. Maternity caregivers are often also reticent about raising the issue of weight with women, even though gestational weight gain is a clinically important issue. The Eating4Two mobile phone app is an intervention that if shown to be effective could be scalable and cost-effectively implemented throughout Australia.

Authors' Contributions

DD drafted the original manuscript. DD, RD, and LTW designed the study and these authors along with CKA and TL contributed to the early work informing this study. All authors read, contributed to, and approved the final manuscript.

Conflicts of Interest

DD, CKA, RD, and LTW developed the app and conducted feasibility testing. There are no other competing interests.

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Abbreviations

ACT: Australian Capital Territory
BMI: body mass index
GWG: gestational weight gain
IOM: Institute of Medicine
SMS: short message service
IRSAD: Index of Relative Socioeconomic Advantage and Disadvantage

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Protocol

The Efficacy of a Web-Based Screening and Brief Intervention for Reducing Alcohol Consumption Among Japanese Problem Drinkers: Protocol for a Single-Blind Randomized Controlled Trial

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Abstract

Background: The literature shows that computer-delivered interventions with personalized normative feedback can reduce problem drinking for up to 6 months in the West. Meanwhile, no studies have been conducted to examine the effects of such interventions among Japanese problem drinkers. Possible moderators associated with effectiveness of the intervention need to be also explored.

Objective: The purpose of this study is to conduct a trial and examine the efficacy of a brief intervention with personal normative feedback and psychoeducation on several measures of alcohol consumption among Japanese problem drinkers. Additionally, this study will examine whether the level of alcohol use disorder and beliefs about the physical and psychological outcomes of drinking moderate the effect of the intervention on outcome measures.

Methods: This study will conduct a single-blind, 2-armed randomized controlled trial. Japanese adults with an Alcohol Use Disorder Identification Test score of 8 or higher will be enrolled in the trial. Participants allocated to the intervention group will receive the intervention immediately after the baseline measurements, and participants allocated to the waitlist group will receive the intervention at the end of the trial. Outcome measures include drinking quantity, drinking frequency, and alcohol-related consequences. Follow-up assessment will take place at 1 month, 2 months, and 6 months following the baseline measurement. The authors will not know the group allocation during trial. The authors will plan to collect a sample of 600 participants. Mixed-effect analyses of variance will be used to examine the main effects of condition, the main effects of time, and the interaction effects between condition and time on outcome variables.

Results: Enrollment for the trial began on January 6, 2018 and data are expected to be available by August 2018.

Conclusions: This study will contribute to the literature by demonstrating the efficacy of Web-based screenings and brief interventions among Japanese problem drinkers and indicating several possible moderators between the intervention and outcomes. This type of Web-based brief intervention has the possibility of being implemented in Japanese schools and workplaces as a prevention tool.

Trial Registration: UMIN Clinical Trials Registry R000034388; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000034388 (Archived by WebCite at http://www.webcitation.org/6xmOoTfTI)

Registered Report Identifier: RR1-10.2196/10650

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Introduction

Background

Globally, alcohol use disorder is a common problem and the World Health Organization has reported that alcohol use is among the top five risk factors for disease, disability, and injury [1], resulting in 5.9% of all deaths [2]. According to a recent survey in Japan, alcohol abuse or dependence ranked as the most common individual disorder with a 7.4% lifetime prevalence, followed by major depressive disorder [3]. Although the Japanese government reports that average alcohol consumption has been decreasing since 1992 [4], 12.7% of males and 3.4% of females in Japan still engage in alcohol consumption of 60g or more, which is considered heavy drinking [3].

Furthermore, alcohol consumption by women has been increasing significantly, and men and women aged 40 to 59 years are particularly vulnerable to risky drinking [5]. However, the rate of individuals seeking and receiving professional help for alcohol-related problems is low. Surveys show that only 16.3% of Japanese individuals with substance use disorders received some form of treatment [6] and, crucially, only 1 in 50 (2%) of people with alcohol use disorders have sought professional help [7].

Computer-delivered Interventions

One recent approach for treating alcohol-related problems is using computer information technology. Computer-delivered interventions have several advantages compared to face-to-face interventions with regard to the reduction of alcohol-related problems. Firstly, computer-delivered interventions have the advantage of user accessibility and the ability to reach a wide population via the internet. Second, computer-delivered interventions can minimize financial costs for the user. Although evidence is limited for alcohol-related problems, computer-delivered interventions have been shown to be relatively cost effective for other mental health problems, such as depression [8]. This approach can also reduce the burden on mental health care professionals. Lastly, the use of computer-delivered interventions reduces the stigma associated with treatments as some users prefer to receive interventions anonymously [9].

Recent studies have shown that internet interventions for alcohol-related problems can be beneficial [10,11], however, the effects of computer-delivered interventions are relatively limited. For example, several systematic reviews and meta-analyses show that computer-delivered screenings and brief interventions reduce alcohol consumption of the participants for up to 6 months, but the effects do not last longer than 12 months [12,13]. A meta-analysis shows multisession interventions have more sustained effects compared with single-session interventions [14], although one study reports no difference between the two types of interventions [15]. When compared to face-to-face interventions, computer-delivered interventions appear to be inferior [16].

Personalized Normative Feedback

Many interventions that have shown the efficacy to reduce alcohol consumption include personalized normative feedback [17,18]. In personalized normative feedback, after users enter information about their demographics and alcohol consumption, they can compare their levels of drinking with the average levels of their age and sex.

Personalized normative feedback thus corrects users' misperceptions of their level of drinking. Internet-based brief interventions with personalized normative feedback have been shown to reduce harmful alcohol use among Canadians [18], indigenous people in New Zealand [19], and Swiss young men [20]. Although effect sizes of these studies are between small and medium [18-20], a meta-analysis supports that personalized normative feedback is effective in reducing alcohol consumption [21].

Because both personalized normative feedback and psychoeducation involve cognitive restructuring regarding drinking patterns, further studies are needed to identify cognitive variables which can increase or decrease the effectiveness of the interventions. Alcohol expectancies are one variable to theoretically explain one's drinking behavior. According to social learning theory, alcohol expectancies are individual beliefs about the effects of drinking on mood and behavior [22]. Alcohol expectancies are associated with frequency and quantity of alcohol consumption [23]. However, the current literature is limited in demonstrating whether the effectiveness of brief internet interventions differs according to the levels of alcohol expectancies.

In Japan, one study found that a psychoeducational video in a classroom setting increased knowledge of alcohol-related problems, but it did not reduce the number of alcohol-related problems among Japanese students in junior college at the 2-month follow up [24]. Although research in computer-delivered interventions has existed for about 20 years, very few computer-delivered interventions for reducing alcohol consumption exist in Japan. To our knowledge no prior studies have examined the effects of internet-delivered interventions using personal normative feedback among Japanese adults with problem drinking.

Purpose of This Study

The first purpose of this study is to examine the efficacy of the Web-based intervention on reducing alcohol consumption among Japanese adults with problem drinking by conducting a pilot trial. To better understand the effects of the intervention, this study will also explore moderators between the intervention and outcome variables such as the degree of alcohol-related problems and participants' beliefs about the effects of alcohol consumption (ie, alcohol expectancies). The authors hypothesize

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that a Web-based intervention will reduce the quantity and frequency of alcohol consumption among Japanese problem drinkers. Additionally, the authors hypothesize that variables such as alcohol-related problems and alcohol expectancies will moderate the effects of the intervention on outcome measures for alcohol consumption. The reduction of alcohol consumption will be greater among individuals with harmful and hazardous levels of drinking than those at the dependent level of drinking. A brief intervention will likely not suffice for individuals with a dependent level of drinking. Moreover, stronger negative or weaker positive beliefs about the effects of drinking will reduce participants' alcohol consumption, due to participants' belief that drinking will lead to negative consequences.

Methods

Description of the Screening and Brief Intervention (Your Health and Alcohol)

The authors have developed a Japanese Web-based screening and brief intervention based on a study conducted by Cunningham et al [18]. The development of the intervention took place between May 2017 and December 2018. This intervention consists of 3 sections: assessment, personalized normative feedback, and psychoeducation. The assessment section asks users to enter their demographic information such as age, sex, height, and weight, as well as average spending on one standard drink (see Multimedia Appendix 1). Users then enter their frequency of typical and heaviest alcohol consumption, the quantity of typical and heaviest alcohol consumption, and different areas of their lives affected by problem drinking over the past 12 months. These measures are partly taken from the Alcohol Use Disorder Identification Test (AUDIT) [25] and the Daily Drinking Questionnaire (DDQ) [26].

The personal normative feedback section of the intervention shows the users' reported drinking level during a typical week, drinking level when they drank the most, frequency of heavy drinking (5 or more drinks in a day), and their AUDIT score. Pie charts and bar graphs are used to compare their levels of alcohol consumption with other individuals of their age and sex (see Multimedia Appendix 2). Estimated annual drinks, the cost of drinking, caloric intake, and areas affected by drinking are also provided. All these results are based on the assessment taken in the first part of the intervention. The reports of other individuals' drinking patterns that users compare with their own were obtained from a previous survey collected from the community using a research marketing company.

The last part of the intervention is psychoeducation about the consequences of problem drinking. This section aims to educate users regarding the recommended amount of drinks (20g per day) according to a report from the Japanese government published by the Ministry of Health, Labor, and Welfare [27]. The process of digesting alcohol and the time it takes to break down alcohol is also provided in this section; based on the weight reported in the assessment section of the intervention, the website calculates the estimated time the user needs to break down consumed alcohol in the body. The website also informs the users about possible physical consequences (eg, damage to the liver, stomach, pancreas, circulatory system, hormones, and brain), psychological consequences (eg, aggression) and social consequences of excessive drinking (eg, increased risk of domestic violence). Information on ways to prevent and reduce problem drinking are also provided for users. Finally, this section includes multiple-choice questions to check how well users understand the psychoeducation materials (see Multimedia Appendix 3).

Trial Setting, Recruitment, and Eligibility Criteria

All participation in the trial occurs online. Recruitment will take place through 2 crowdsourcing websites and 1 research marketing company. The authors used this online recruitment method since the population receiving this intervention are likely to be frequent internet users. Individuals registered on the systems will be asked to participate in the study through the posted URL. The URL will direct participants to a website created specifically for this trial. The inclusion criteria for participation is scoring 8 or higher on AUDIT [25] and being aged 20 years or over.

Procedure and Allocation

Once participants are directed to the trial website, they will first take the screening measures (ie, AUDIT), and only those who meet the eligibility criteria will be invited to formally participate in this trial. Participants who do not meet the eligibility will be directed to a webpage showing that they are not eligible to participate in the study, whereas those who meet the criteria proceed to the next section without being told the screening results. Participants will be asked to spend between 5 and 15 minutes entering their typical drinking patterns and to think about their results and alcohol-related health. After participants fully read and understand the nature of this study, and consent to participate in the trial, they will be asked to enter their email address or their account name on the crowdsourcing site to receive notifications for subsequent follow-ups. They will then provide their demographic information and complete the measures of alcohol expectancies.

This study will be a 2-armed randomized controlled trial. Participants will be randomly allocated to either the intervention group or the control group. The website created for this trial automatically allocates participants to either group using computer-generated numbers. Both groups will complete the assessment part of the intervention. Only the intervention group will receive the personalized normative feedback and psychoeducation immediately after the baseline measures. The control group is the waitlist group of participants who will be notified that they will receive the intervention at the end of the participation.

Figure 1 shows the flow of the trial. Participants will complete the outcome measures at baseline, 1 month, 2 months, and 6 months into the study. At each follow-up, participants will be asked to enter information about their drinking patterns since their last assessment. Specifically, they will be asked about their drinking patterns during the past month at the 1-month and 2-month follow-ups and their drinking patterns over the past 4-months at the 6-months follow-up (due to the previous assessments being conducted 1 and 4 months prior respectively).

At the end of the trial participation, the participants will be thoroughly debriefed about the nature of the study. Participants registered in the research marketing company will be compensated with ¥120 (equivalent to US $1) and 1000 credits. Participants on the crowdsourcing website will receive ¥1200 (equivalent to US $11) as work compensation after completing all the follow-up measures.

Interventions

This study will use the Web-based intervention (Your Health and Alcohol) developed prior to the trial (see above for the description of the intervention).

Measures

Primary outcomes are the quantity of weekly alcohol consumption, quantity of largest alcohol consumption on one occasion, and frequency of drinking. The secondary outcome is the different areas of life which their drinking has affected. These measures are partly taken from the AUDIT [25,28] and DDQ [26] questionnaires and they have been previously used in other trials [18-20].

To investigate possible moderators between the intervention and outcome measures, the participant's level of alcohol-related problems will be categorized as hazardous, harmful, and dependent according to their levels of AUDIT score [29,30]. Another measure is alcohol expectancies. In this measure, alcohol expectancies are defined as beliefs about physical and psychological effects of alcohol consumption [31]. Positive aspects of alcohol expectancies are mood enhancement and stress coping, and negative aspects of alcohol expectancies are physical ailments and dysphoria.

Participant Timeline

Enrolment for this trial began on January 6, 2018.

Figure 1. A CONSORT flowchart for the trial.
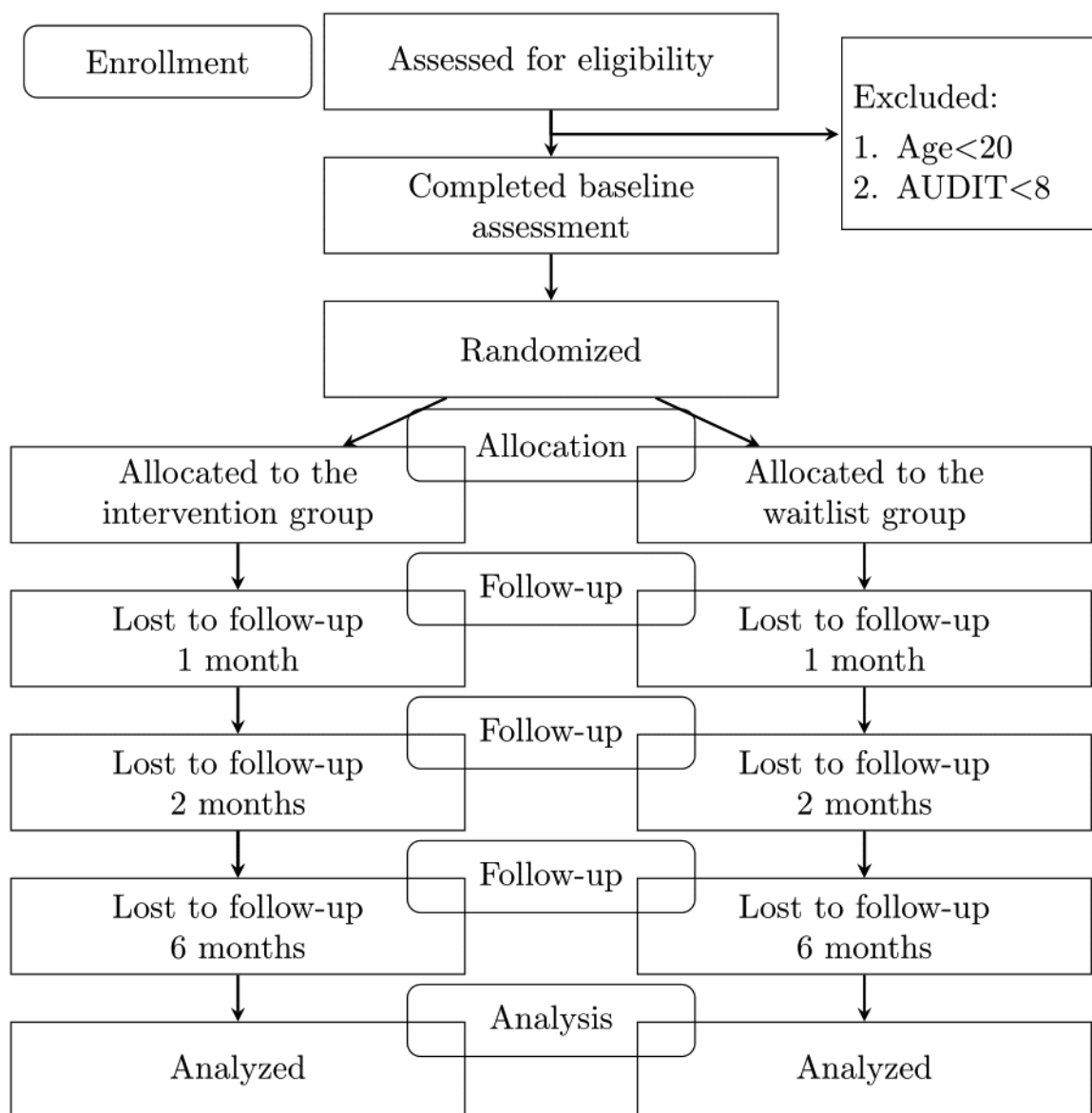
Blinding

At the beginning of the study, participants are informed that they will receive the intervention either immediately after the baseline or at the end of the trial. Meanwhile, all instructions to participants are uniform, and the authors will not know the participants' allocation during trial.

Ethical Procedures and Possible Harm

The research ethics board at the first author's university approved the current study (approval #17-174). All procedures are according to the UMIN Clinical Trial Registry (R000034388) and follow the guidelines of Standard Protocol Items: Recommendation for Interventional Trials [32]. The authors anticipate the possible harm of this intervention is minimal because participants will simply receive information related to alcohol consumption. If participants experience distress and require professional assistance during the trial, the authors will refer them to appropriate treatment.

Power Analysis

Previous studies have suggested small effect size for internet-based interventions for drinking consumption (1 drink less per week) [12]. A power analysis was conducted in R (software for statistical computing) and found that to obtain statistically significant results a total sample of 393 is necessary for 80% statistical power at $P<.05$ for significance level. One trial conducted in Japan reported a 65% dropout rate [33]. Because a high attrition rate is expected in internet-based research, the authors will collect a sample 600 of participants.

Data Monitoring, Auditing, and Management

Since the intervention is a single session immediately subsequent to the baseline, the authors have determined that monitoring of participants' reporting or interim analyses to continue or discontinue with the trial is not necessary. The authors do not plan to ask a third-party to audit the trial. All consent forms and private or identifying information will be separated during data analyses to protect anonymity.

Statistical Analyses

To evaluate the feasibility of the website intervention, the authors will review participants' comments about the intervention. Additionally, the authors will calculate the attrition rate from the enrollment to the final assessment. All data analysis will be performed in R [34]. First, descriptive statistics will be calculated to show the mean and standard deviation of measured variables. Data will be screened for missingness, outliers, linearity, normality, and homoscedasticity. Appropriate data transformation will be used for subsequent data analyses. Intention-to-treat analyses will be conducted to examine the efficacy of the intervention on all outcome measures. Missing data will be replaced with multiple imputations.

Linear mixed-effect model analyses of variance (ANOVA) will be used to examine the main effects of condition, the main effects of time, and the interaction effects between condition and time of the intervention on outcome measures. To examine the moderating variables between the intervention and outcome measures, alcohol expectancies and levels of AUDIT will be separately added into the model. Interactions of alcohol expectancies or AUDIT with condition, time, and condition × time (multiplying the two) will be analyzed. An R package called "nlme" will be used for these analyses [35].

Results

Recruitment began on January 6, 2018, and data are expected to be available for analyses by November 2018.

Dissemination Policy

Once data collection and analysis are completed, the authors will prepare a manuscript to publish the results in an academic journal. The authors plan to disclose the protocol or the results in first author's academic thesis, academic conferences, and the journal in which the manuscript will be published.

Discussion

Overview

The purpose of this study is to conduct a single-blind 2-armed pilot randomized controlled trial to examine the efficacy of the website intervention for 6 months for reducing alcohol consumption among Japanese problem drinkers. This study will collect data using two different crowdsourcing websites and one research marketing company. Instructions are given uniformly throughout the trial, and thus the authors will not know the allocation of the participants. Data collection is expected to end in late 2018. The authors hypothesize that the intervention will have significant effects with a medium or small effect size consistent with a similar previous study [18-20]. The effect size will likely decrease over time but may last up to 6 months, since the literature shows that the effects of computer-delivered interventions do not last for longer than 6 months [12,13,36]. The authors hypothesize that alcohol expectancies will moderate the effects of the intervention on the outcome measures. Additionally, the authors expect that the levels of the AUDIT scores will moderate the effects of the intervention on the outcomes. Participants at the harmful and hazardous level of the AUDIT score will show larger effects from the intervention than those at the dependent level. These individuals with the dependent level will require more extended internet or face-to-face interventions.

Limitations

This study comes with several limitations. The first limitation is accuracy of item responses. Converting alcohol consumption to a standard measure of drink will be an unfamiliar task for many Japanese individuals, and they may not report their AUDIT or the screening items accurately. For a second limitation, a sampling bias may exist because this study will recruit only individuals who are registered in a specific research marketing company or participating crowdsourcing websites. This sample may have different characteristics from those in the general population in Japan. Many of them are likely freelance workers working independently as opposed to belonging to a company or organization. This demographic difference may affect results of this study in terms of drinking as opportunities for social engagement. Social drinking is a

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common practice in Japan, and results of this study may not fully capture this drinking pattern.

Additionally, literature shows that internet-based studies commonly encounter high drop-out rates and inattentive responses during trial [33,37]. When a substantial portion of participants drop out of the study, this study can only reveal results of those who adhere to the intervention. This study is unable to reveal effects of the intervention among participants who discontinue with the study.

Implications of the Study and Suggestions for Future Studies

As previous studies have revealed that seeking alcohol treatment is unpopular in Japan [3], computer-delivered interventions will play an important role for reducing alcohol consumption. To our knowledge this is the first study to examine the efficacy of an internet intervention with personalized normative feedback among Japanese problem drinkers. The authors argue that a Web-based screening and brief intervention can be useful to implement in various settings such as university or workforce. Since the legal drinking age is 20 in Japan, many university students are at risk of underage drinking and thus alcohol-related problems. This study excluded individuals engaging in underage drinking because of ethical responsibility. However, future studies may examine the efficacy of the intervention among university students by including students engaging in underage drinking. One study reports more than half of the students engaging in underage drinking in Japan [38]. Also, statistics show that in Japan men aged between 40 and 60 have the highest alcohol consumption compared to men in other ages or women [5]. Interventions with personalized normative feedback and psychoeducation can be used as a preventative tool before students or workers develop serious problems.

The literature shows ample evidence that alcohol expectancies are associated with drinking behavior [39]. Examining alcohol expectancies as possible moderators between effects of interventions and drinking behavior can contribute to the literature by applying theoretical understanding of drinking patterns into clinical settings.

Although more smartphone-delivered interventions have been used in recent approaches, the present study utilized a laptop or desktop computer. Users are likely in a less distracted environment when sitting in front of a laptop or desktop. Also, users can check the report from the intervention easily with a wider screen. However, future studies may develop a brief intervention using a mobile device and take advantage of its supporting functions.

The literature indicates that single-session interventions have limited effects on alcohol-related problems [40]. Future studies need to develop more rigorous interventions which improve the magnitude and duration of the effects. Previous studies have shown that extended multiple interventions have sustained effect sizes compared with single-session interventions [14]. Although this study offers only a brief single-session intervention, extended and theory-based computer-delivered interventions would provide added benefits for reducing alcohol-related problems.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Assessment in the Intervention.

[PNG File, 228KB - resprot_v7i5e10650_app1.png]

Multimedia Appendix 2

Personalized Normative Feedback in the Intervention.

[PNG File, 164KB - resprot_v7i5e10650_app2.png]

Multimedia Appendix 3

Psychoeducation in the Intervention.

[PNG File, 438KB - resprot_v7i5e10650_app3.png]

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Abbreviations

AUDIT: Alcohol Use Disorder Identification Test
DDQ: Daily Drinking Questionnaire

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Protocol

A Participatory Health Promotion Mobile App Addressing Alcohol Use Problems (The Daybreak Program): Protocol for a Randomized Controlled Trial

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Abstract

Background: At-risk patterns of alcohol use are prevalent in many countries with significant costs to individuals, families, and society. Screening and brief interventions, including with Web delivery, are effective but with limited translation into practice to date. Previous observational studies of the Hello Sunday Morning approach have found that their unique Web-based participatory health communication method has resulted in a reduction of at-risk alcohol use between baseline and 3 months. The Hello Sunday Morning blog program asks participants to publicly set a personal goal to stop drinking or reduce their consumption for a set period of time, and to record their reflections and progress on blogs and social networks. *Daybreak* is Hello Sunday Morning's evidence-based behavior change program, which is designed to support people looking to change their relationship with alcohol.

Objective: This study aims to systematically evaluate different versions of Hello Sunday Morning's *Daybreak* program (with and without coaching support) in reducing at-risk alcohol use.

Methods: We will use a between groups randomized control design. New participants enrolling in the *Daybreak* program will be eligible to be randomized to receive either (1) the *Daybreak* program, including peer support plus behavioral experiments (these encourage and guide participants in developing new skills in the areas of mindfulness, connectedness, resilience, situational strategies, and health), or (2) the *Daybreak* program, including the same peer support plus behavioral experiments, but with online coaching support. We will recruit 467 people per group to detect an effect size of f=0.10. To be eligible, participants must be resident in Australia, aged ≥18 years, score ≥8 on the alcohol use disorders identification test (AUDIT), and not report prior treatment for cardiovascular disease.

Results: The primary outcome measure will be reduction in the AUDIT-Consumption (AUDIT-C) scores. Secondary outcomes include mental health (Kessler's K-10), days out of role (Kessler), alcohol consumed (measured with a 7-day drinking diary in standard 10 g drinks), and alcohol-related harms (CORE alcohol and drug survey). We will collect data at baseline and 1, 3, and 6 months and analyze them with random effects models, given the correlated data structure.

Conclusions: A randomized trial is required to provide robust evidence of the impact of the online coaching component of the *Daybreak* program, including over an extended period.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12618000010291; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373110 (Archived by WebCite at http://www.webcitation.org/6zKRmp0aC)

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KEYWORDS

alcohol drinking; internet; evaluation studies; social marketing; health promotion

Introduction

Globally, 5.9% of deaths are attributed to alcohol consumption, and 5.1% of the global burden of disease and injury is attributed to its use [1]. In Australia, alcohol consumption is estimated to cause 3.2% of the total burden of disease. Including harms to nonusers, alcohol consumption contributes about 188,000 disability-adjusted life years, causes 5550 deaths, and costs approximately AU $30 billion/year [2,3]. Australian guidelines provide recommendations for the general adult population specifying that, to reduce the risk of alcohol-related harm over the lifespan, average consumption should be 2 or fewer drinks per day. To reduce the risk of injury from a single occasion of drinking, 4 or fewer drinks are recommended. Further, more stringent recommendations are made for specific groups (eg, pregnant women, those with a family history of alcohol disorders) where the risk of alcohol-related harms is greater [4].

Considered against the 2 main guidelines, in 2016, about 17% of adults were at-risk from their average alcohol consumption, about 26% from their single-occasion use [5], and 37% from either single occasion or average use [6]. Notably, most alcohol-related harm arises from those who consume in an at-risk manner rather than those with an alcohol disorder, with a much greater number of at-risk drinkers than those with disorders [7]. Furthermore, less than 17% of those with an alcohol disorder ever receive treatment for their condition [8], and among those people with less severe alcohol problems, most are unlikely to seek help for their drinking [9].

One approach to addressing alcohol use among those with less severe problems is opportunistic screening and brief intervention (SBI), with the evidence base for the effectiveness of SBI being substantial [10-13]. Under the rubric of SBI, programs can range from a simple screening question combined with a minimal amount of feedback, eg, normative data on alcohol use, through to the use of standardized screening instruments and more intensive interventions that can include components of motivational interviewing and cognitive behavioral therapy. Typically, SBI can be incorporated into a single treatment session in a few minutes but can be several sessions lasting a few hours [14]. However, some, but not all, studies suggest that SBI may be more effective with males than females, and there is an absence of evidence for their effectiveness for those with more severe alcohol use problems [10,11,15]: these people are typically referred for more intensive treatment [16]. Overall, SBI does not appear to have been widely adopted into primary care, and questions remain about its practical implementation, especially within the context of the Australian drinking culture [17,18].

Therefore, alternative approaches to complement existing programs are required. Web-based SBI alcohol interventions have been developed, evaluated, and found to be effective in both college student samples and the general public, excluding students [19,20], with typical effects in the small to medium range (eg, effect size g=0.20-0.44) [19,21]. Web-based interventions in their briefest form (eg, single session) typically rely on normative feedback on the self-reported quantity of alcohol consumed, whereas more complex interventions may involve multiple sessions and draw on a range of psychological approaches including motivational enhancement, cognitive behavior therapy, and behavioral control [19,21], similar to the components used in traditional SBI. Nevertheless, Web- or mobile-based SBI has potential advantages over traditional formats, including extended reach, anonymity, timely accessibility, treatment fidelity, the potential to model behavior, and access without the involvement of professionals [21,22]. The evidence to date for the effectiveness of mobile phone–based alcohol interventions is inconclusive, with outcomes ranging from significant improvements on some alcohol measures to significant declines on other measures [23,24].

The benefits of including additional resources to support internet-based interventions are currently unclear. A meta-analysis of internet interventions for depression found a large effect size (g=0.78) [25], where all except one of the studies included therapist support. In contrast, a meta-analysis of self-guided internet interventions for depression reported a small effect size (d=0.28) [26]. However, a comparison of alcohol interventions found no significant difference between guided (effect size g=0.23) versus unguided (effect size g=0.20) interventions, although the authors note that this may be due to the small number of guided studies [19]. Nevertheless, benefits have been shown in improving alcohol outcomes (and other health behaviors) from using multiple modes of delivery such as text messages, drawing on theoretical models, and incorporating multiple behavioral change techniques [27,28].

Observational data show that a person's social network can either increase or decrease their alcohol use [29]. Social networks now include those formed on the internet. These sites range from simple bulletin boards through to virtual lives, but typically allow users to post blogs (text) and images that stimulate discussion and the formation of social groups [30]. The effects of these networks on behavioral change have been evaluated with inconsistent effects found with respect to diet and exercise [31], but to date, the effectiveness of social networks in reducing alcohol consumption has not been determined [30,31], but it is currently being trialed in youth with depression and who engage in binge drinking [32]. In contrast, the persuasive effects of Web-based social networks have been extensively harnessed by alcohol brands to engage with alcohol consumers, with some brands having attracted millions of followers [33,34]. This trial will evaluate the

effectiveness of the online coaching component of Hello Sunday Morning's *Daybreak* program and associated support as a means of reducing alcohol consumption.

Hello Sunday Morning is an Australian social media health promotion movement that asks participants to publicly set a personal goal to stop drinking or reduce their consumption for a set period of time (typically 3, 6, or 12 months [35]), and to record their reflections and progress on blogs and social networks [35,36]. The platform was created in 2010, with the aim of motivating members and holding them accountable by asking them to set a public goal. Further development included gamification features, which were structured games that facilitated participation and engagement with the internet community. Participants in the legacy Hello Sunday Morning platform were recruited by social marketing tactics, leveraging the idea of a movement toward a better drinking culture through social media, word of mouth, and a television commercial. A large portion of members were also recruited through Google AdWords. This platform is no longer actively recruiting participants, and as such individuals are now directed toward the *Daybreak* program.

Initial research conducted on the platform explored the blog content and qualitative reports of change. Text analytics of the blog posts on the platform show that participants typically begin with descriptions of their drinking practices, which over time change to posts reflecting their efforts to change their behavior [37]. Research on the Australian users has found that 84% of participant's report completing the program time they signed-up to without a slip-up, defined as drinking alcohol before finishing. These participants reported reduced alcohol use and desire to drink alcohol for fun or to relieve tension, and improved mental health [38]. Participants have also reported feeling more positive about themselves, improved productivity and engagement in new activities, as well as new and/or improved relationships and financial savings [39].

Australian users of Hello Sunday Morning are more likely to be female (61%) than male, with most aged less than 50 years (89%). Few (5%) are classified as low-risk alcohol users as assessed by the alcohol use disorders identification test [40] (AUDIT) (score=0-7), with 42% classified in the hazardous or harmful range (AUDIT 8-19) and 53% classified as probably dependent (AUDIT≥20) [35]. Limited follow-up data (n=49) on a subsample of Victorian Hello Sunday Morning participants (n=345) found that the prevalence of probably dependent drinkers fell from 45% at baseline to 7% at 1 month and 24% at 3 months [41].

The aim of the study was to evaluate the effectiveness of the online coaching component of the *Daybreak* program in reducing alcohol consumption via a randomized controlled trial. The *Daybreak* program is a smartphone app developed by Hello Sunday Morning, based on the original Web-based program. *Daybreak* consists of the same social-networking peer-support forum as the Hello Sunday Morning program but also includes clinically based activities known as behavioral experiments and chat-based coaching. The primary hypothesis is that those randomized to receive *Daybreak* including peer-support, behavioral experiments (see *Content of the interventions* for

details) plus online coaching, will show a greater reduction in alcohol-related problems that those randomized to just access the *Daybreak* program including peer-support and behavioral experiments (without online coaching). Consistent with the literature, the secondary hypotheses are that greater improvements will be shown for those with lower AUDIT scores (8-19), than those in the higher score category (≥20), and finally, greater improvements are expected for male participants [15,42].

Methods

Design

We will use a randomized control design to compare (1) the *Daybreak* program including peer support, behavioral experiments plus online coaching or (2) *Daybreak* program including peer support and behavioral experiments. (The content of the interventions are described below.) Outcome data will be collected at 1, 3, and 6 months post enrollment in the study with all groups receiving the same schedule of assessments (Figure 1). Australian ethical guidelines preclude the use of placebo (no treatment) control groups where a risk has been identified and there are existing treatments/interventions [43].

Participants and Randomization

All new registrants to *Daybreak* will receive information about the study: it is anticipated that no additional advertising will be required. To be eligible for the study, participants must be aged 18 years or older, score 8 or more on the [44] AUDIT, and be resident in Australia. Participants also require a valid email address and access to the internet. We will exclude those who have ever received treatment for cardiovascular disease, due to the risks for this latter group [45]. In addition, the screening questions include the P4 suicidality screening survey [46]. Those scoring above minimal risk will still be eligible for the study but will receive details of a national, 24-hour crises support line (lifeline).

Regardless of the group to which they are randomized, those scoring 20 or more on the AUDIT (probable dependence) will be eligible for inclusion in the study but will also be advised to seek in-person guidance from their general practitioner or other clinician before reducing their alcohol consumption, to minimize the risk of serious complications from alcohol withdrawal. Given the large sample, simple fully automated randomization will be implemented. Participants will be blind to their group allocation—all will receive an active treatment. Participants access the platform by logging in with their email address and password.

Procedure

Enrollment and intervention procedures will be self-guided. Individuals who register to start the *Daybreak* program generate a username and password, and they will then be asked if they are interested in participating in the project. For those affirming, they will then receive the full study description and be asked for active consent (clicking on a button). They will then be screened for eligibility by completing a Web-based survey, before being randomized. Those that are screened as ineligible are returned to the *Daybreak* on-boarding procedure (Multimedia Appendix 1) and notified of their ineligibility, and they are

provided with relevant details of the crisis support services. Participants have unlimited access to their respective areas, and those randomized to *Daybreak* plus coaching can access a health coach (available from 7 AM to 7 PM local time Monday-Friday).

At 1, 3, and 6 months, participants will be emailed and texted a link to the follow-up survey. If they do not complete the survey, a repeat text message will be sent 1 week later. Following this, a research assistant (blind to group allocation) will call the participants to remind them to complete the survey on a maximum of 3 occasions and provide the link again via email or text message if requested during the call. At each wave, participants will be invited to enter their details for a prize draw to win an iPad 2. Participants do not have to complete the survey to enter the draw, but the link to the prize draw will be at the end of the surveys. The study received institutional ethics approval (2017-0855) and has been registered with the Australian and New Zealand Clinical Trials Registry trial number ACTRN12618000010291.

Recruitment will be conducted over 10 months from February to November 2018 or until the desired sample size is obtained. New registrants either directly download the *Daybreak* app from the App Store, or reach the Hello Sunday Morning website (where they are directed to download it) by searching Google, or by clicking from other websites such as healthdirect.gov or other health service directories, or by clicking through from the Hello Sunday Morning email newsletter.

Sample Size

We are unaware of any prior studies using social networks for alcohol reduction, but for other behaviors, the reported changes are small but not significant [31].

Figure 1. Flowchart of participants through the trial.
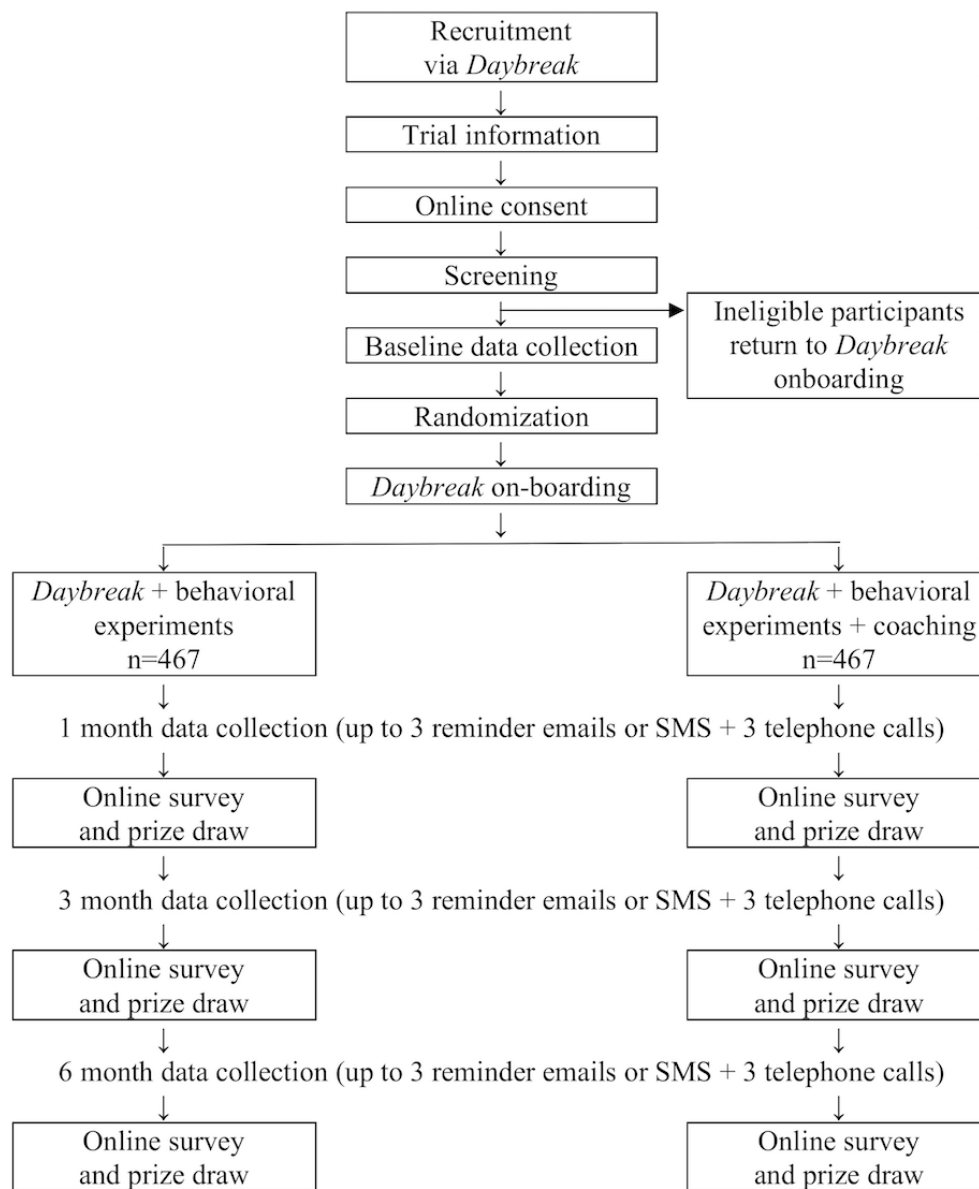
The effect sizes for Web-based SBI alcohol interventions are in the range d=0.3-0.4 at 6 months [19-21]. On the basis of a small estimated effect size of f= 0.10 (equivalent an effect size of d=0.2) at 6 months, with a correlation between repeated measures of r=0.5, we will require 60 people per group for the main analysis based on power of 0.80 and alpha set to P<.05. Given the interest in the effectiveness of interventions by gender and for those with probable dependence (assessed via the AUDIT), the objective will be to recruit approximately 60 people in the smallest cell(s). From demographic data [35] with about 50% of the *Daybreak* population likely to be in the probable dependence AUDIT category and 40% being male, to obtain about 60 people in this cell will require 300 people per study arm (600 in total). To allow for attrition, the target will be to recruit 467 per arm (N=934), with 35% lost to follow-up.

Outcome Measures

All measures will be assessed at each time point except the AUDIT (baseline only) and adverse events [47] (baseline and the final time point; see Table 1). The primary outcome will be change in AUDIT-consumption (AUDIT-C) scores. The AUDIT was developed by the World Health Organization and validated in a range of countries, including Australia [44]. It has a range of 0-40: a threshold of 8 or more will be used as a screening measure to identify eligible participants at baseline. With follow-up at 1, 3, and 6 months, the change in the first 3 questions (known as the AUDIT-C) will be the primary outcome and used to assess change in alcohol use (as some of the other AUDIT questions use a reference period of the last 12 months). The AUDIT-C has also been shown to predict clinical outcomes at 1 year [48]. The secondary outcomes will be changes in:

1. Alcohol consumption assessed with a 7-day drinking-diary [49,50].
2. Kessler's K-10 is a brief screening instrument for psychological distress and also a treatment outcome measure [51]. Scores range from 10 to 50, with scores of 20-24 interpreted as showing a mild distress, 25-29 a moderate distress, and 30-50 showing a severe mental health distress.
3. Kessler's Days out of role [52] will be used to quantify days either completely or partially out of role in the previous 30 days and the number of these due to alcohol use. Those with alcohol dependence have significantly more days completely or partially out of role than those without a disorder. Similarly, those with comorbid substance use and anxiety disorders or substance, anxiety, and affective disorders have increased days out of role [52].
4. Health resource use will be assessed with a checklist of medical and other health professionals consulted in the last 8 weeks and adapted from an existing checklist [53] to include alcohol or other drug treatment services and alcohol pharmacotherapy.
5. The global rating item from the Pittsburgh Sleep Quality Index will be used to categories sleep quality on a 4-point scale (very bad-very good) in the previous month [54].
6. The 3-item Godin Leisure-Time Exercise questionnaire will be used to quantify the frequency of spending 15 minutes or more engaged in each of 3 levels of exercise intensity (strenuous, moderate, and light) in the last 7 days [55].

7. Quality of life will be assessed with the 8-item EUROHIS-QoL that has been validated in Australia [56] and is recommended for use in alcohol and other drug treatment services [57].
8. Adverse events associated with alcohol use will be assessed at baseline and 6 months with the checklist from the Core alcohol and drug survey [47]. It was designed specifically for college populations, so 2 items specially referencing this setting were modified (ie, "missed a class" changed to "missed a class or work" and "been in trouble with police, resident hall, or other college authorities" changed to "been in trouble with police or other authorities"). Given the focus on alcohol, we deleted the reference to drug use from the lead in statement and from 1 item ("Thought I might have a drinking or other drug problem"). Among college students in the United States in the previous 12 months, more than one-third reported driving under the influence and 20%-30% had been in an argument or fight.

Content of the Interventions

The *Daybreak* program is designed for people looking to change their relationship with alcohol. It allows participants to set a goal, reflect on their mood, and engage with peer support. *Daybreak* helps people to change their relationship with alcohol in 4 ways.

The first one is weekly check-ins. *Daybreak* supports members in a self-reflection process to discover their inner drivers. With the help of Australia's leading experts in motivational interviewing, *Daybreak* has created a set of self-report questionnaires (Multimedia Appendix 2) that are designed to help people uncover their intrinsic motivators for change.

The second one is peer support. *Daybreak* connects members to the *Daybreak* Community, a channel to immediate empathy, problem solving, and accountability. Currently, 45% of shares in *Daybreak* receive 5 or more comments within an hour. The program supports a vibrant community with members who care for each other, help each other navigate tough times, and keep each other in check.

The third one is behavioral experiments. *Daybreak* encourages members to take experiments and reflect on their learnings. Designed by the Hello Sunday Morning Clinical Team, these experiments draw on techniques from cognitive behavioral therapy, motivational interviewing, and acceptance and commitment therapy. There are a range of experiments across 5 areas including mindfulness, connectedness, resilience, situational strategies, and health. Mindfulness experiments help members learn how to be in-the-moment and recognize when a drinking trigger has been activated. The connectedness experiments help them to connect with others in a meaningful and healthy way without alcohol. The resilience experiments teach them how to bounce back from negative experiences and lapses. The situational experiments provide strategies for a range of common trigger situations. Finally, the health experiments assist members in establishing good fitness routines, good eating and sleeping habits, and general health strategies to help with regulating mood (Figure 2).

The fourth one is health coaches. All health coaches meet the low-intensity mental health guidelines set by the Australian Government Department of Health [58]. Specifically, this includes a minimum certificate IV in a mental health or community services discipline. The clinical team of health coaches at Hello Sunday Morning all meet this minimum criterion, as well as having specific alcohol and other drug training and experience. Some coaches are registered General and Clinical Psychologists.

Health coaches are required to undertake in-house training, which includes modules on health coaching and how it differs from therapy, ethical considerations when providing Web-based services, alcohol facts and management strategies, forming connections during online support, motivational interviewing, case studies and ethical dilemmas, coaching procedures, risk management, as well as platform-specific training modules. They undergo a period of supervision on initial interactions with participants and then periodically receive feedback from a senior health coach. Health coaches also participate in fortnightly peer supervision for case discussion and receive individual supervision with an Australian Health Practitioner Regulation Agency–approved supervisor who is a clinical psychologist, when needed.

Health coaches partner with members to help them set and reach goals for satisfying and healthy lives. The coaching service is conducted via real-time chat-based messaging on a secure platform. Health coaches again use cognitive behavioral therapy, motivational interviewing, and acceptance and commitment therapy techniques. Coaches tailor support and the approaches used to suit the member's needs.

Analysis

We will evaluate the primary and secondary outcome using an intention-to-treat approach with the effect of the intervention on each measure being assessed via a time-by-group interaction. Due to the correlated data arising from the repeated measures, we will employ a multilevel mixed effects regression model with a random intercept term. This will control for clustering of variance within individuals over the repeated measures. For continuous data, we will use an unstructured correlation matrix with a normal distribution and identity link. For other types of data (eg, count, categorical), multinomial, Poisson, or negative binomial distribution will be used with their appropriate link functions. A sensitivity analysis will include use of specialist alcohol services or alcohol pharmacotherapy as a covariate.

Participant Safety

There are a number of mechanisms in place for forum monitoring (eg, blog posts and comments). The first is an automated system that alerts the clinical team when a member writes a post including a trigger word and receives more than 30 comments. Trigger words are predetermined words that may indicate a member is at risk (eg, kill, suicide, hurt, end it, no meaning, hopeless, cannot cope, die). Second, the forum is monitored by support staff and the clinical team, who will intervene on a thread if needed and contact the member privately via email. Third, members are able to report posts to *Daybreak* administration if they are concerned about a member or their post.

The existing *Daybreak* Risk Management Protocol will be used for all participants in the *Daybreak* research trial who report serious mental health concerns, suicidality, self-harm, family violence, or risk to children. Although there are procedures in place for each concern, they typically include working collaboratively with the member to keep them safe, deescalating the situation and implementing a safety plan, as well as encouraging them to contact suitable referrals (eg, specific or face-to-face services) provided by health coaches.

Table 1. Data collection schedule.

Measure	Baseline	1 month	3 months	6 months
Demographics	✓			
Drinking diary	✓	✓	✓	✓
AUDIT[a]	✓			
AUDIT-C[b]	✓	✓	✓	✓
K-10[c]	✓	✓	✓	✓
Days out of role	✓	✓	✓	✓
Health resources	✓	✓	✓	✓
Sleep quality	✓	✓	✓	✓
Exercise	✓	✓	✓	✓
Quality of life	✓	✓	✓	✓
Adverse events	✓			✓

[a]AUDIT: alcohol use disorders identification test.

[b]AUDIT-C: alcohol use disorders identification test-consumption (items 1-3).

[c]K-10: Kessler 10.

Figure 2. Example of Daybreak behavioral experiments.
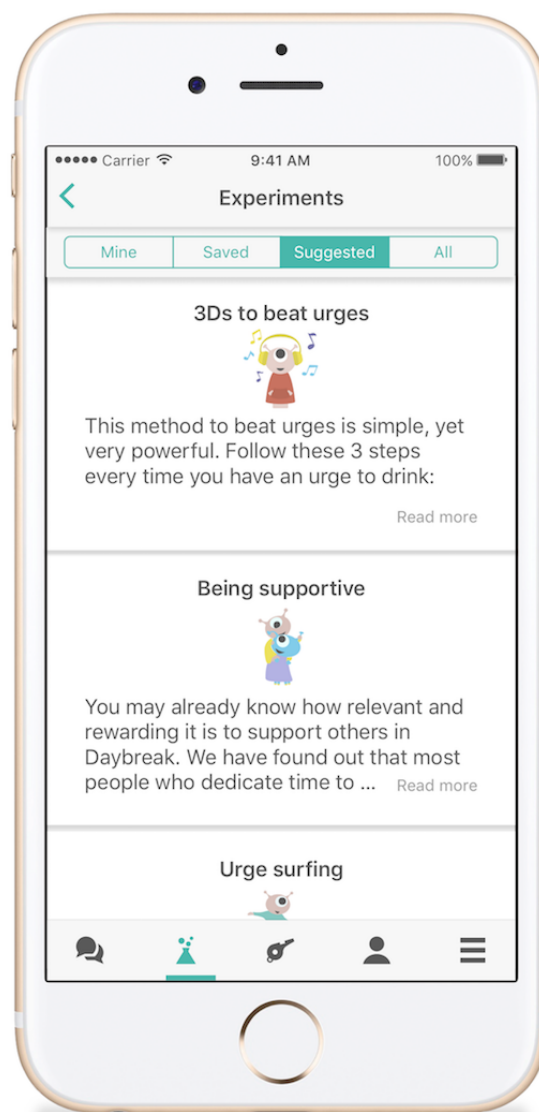
The Hello Sunday Morning site and intervention are not designed to provide support for emergency situations, such as severe withdrawal symptoms (seizure or delirium tremens) or severe psychological distress. In a general hospital sample, 0.65% incurred either a seizure or delirium tremens [59], but in an alcohol detoxification inpatient sample, 5.6% had delirium tremens and 7.4% had seizures [60]. Therefore, anyone scoring 20 or more on the AUDIT will be advised to seek medical guidance before reducing their alcohol use. We will also recommend that anyone who has ever incurred a seizure or delirium tremens seek advice. In addition, we will provide details of national hotlines for psychological problems.

Results

Enrollment of participants started in February 2018, with recruitment projected to be completed in November 2018, with the 6 month follow-up completed by the end of May 2019. Data analysis has yet to start.

Discussion

To the best of our knowledge, this will be the first formal evaluation of the effectiveness of a smartphone-based peer support platform with coaching in reducing alcohol consumption and associated harms. It will assess critical, clinically relevant outcomes, including changes in alcohol consumption and improvements in mental health and quality of life. The minimal use of incentives in the project design will mean that the findings will be generalizable to real-world settings, with the long period of follow-up important in establishing the persistence of any behavioral changes.

Currently, there is no definitive evidence to support the effectiveness of standard brief interventions among those with more severe alcohol disorders, with equivocal findings for both reductions in alcohol use and improving treatment seeking [15]. Nearly half of Hello Sunday Morning participants score in the probable dependence range on the AUDIT [35], so the outcomes for this subgroup of participants is of particular importance in addressing the gap in the provision of effective alcohol consumption interventions.

The study has been powered to detect effects within critical subgroups, namely, those with people with potential alcohol dependence and by gender. Therefore, in addition to reporting statistical significance results for the main analyses, which may represent trivial changes given the overall size of the sample, we will report effect sizes and discuss effects in terms of their clinical significance, eg, changes in categorical levels on the K-10 and AUDIT.

With respect to the continuing provision of the service, *Daybreak* is a service of the organization Hello Sunday Morning, which is funded through a range of commercial and corporate partnerships, grants, and government contracts. These will allow ongoing dissemination of the service including hosting the program and funding its health coaches. If successful, outcomes of the study will be used to advocate for further funding and wider dissemination via other sites, such as general practitioners and hospital emergency departments.

The study raises some ethical issues, particularly with respect to the age of participants and the adverse outcomes that can occur in unsupported withdrawal from alcohol use. Although we will ask participants to confirm that they are aged 18 years or older, and thus able to provide informed consent, the noninvasive nature of the intervention reduces the concerns about underage participants entering the trial. To mitigate against the potential for unsupported severe withdrawal symptoms, we will advise participants considered to be at higher risk to seek professional guidance before reducing or ceasing consumption.

The study relies on self-reported data, which is common for Web-based alcohol interventions [19]. Other than the identification of acute intoxication, objective quantification of alcohol use even over a limited period (such as 7 days) is difficult. None of the standard clinical markers (eg, gamma glutamyltransferase) perform adequately as screening tests for this task, particularly with women and at intermediate levels of alcohol use, or provide a quantification of the amount of alcohol consumed [61]. Therefore, we believe that there is no other method of determining the extent of alcohol use that is more reliable than self-report, without implementing far more demanding procedures, such as twice daily breath testing, as used in some judicial programs [62].

Acknowledgments

Conflicts of Interest

JJLK is employed by Hello Sunday Morning. Neither RJT nor MPS have any conflict of interest to declare.

Multimedia Appendix 1

On boarding questionnaire and feedback at sign up.

[PDF File (Adobe PDF File), 164KB - resprot_v7i5e148_app1.pdf]

Multimedia Appendix 2

Weekly review questionnaire.

[PDF File (Adobe PDF File), 41KB - resprot_v7i5e148_app2.pdf]

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Abbreviations

AUDIT: alcohol use disorders identification test
AUDIT-C: AUDIT-consumption
K-10: Kessler 10
SBI: screening and brief intervention

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Protocol

Thrive With Me: Protocol for a Randomized Controlled Trial to Test a Peer Support Intervention to Improve Antiretroviral Therapy Adherence Among Men Who Have Sex With Men

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Abstract

Background: The suboptimal rate of viral suppression among persons aged 13 years and older and residing in 37 states and the District of Columbia leaves considerable opportunities for onward transmission and contributes to poor health outcomes. Men who have sex with men (MSM) represent one of the most at-risk groups in the United States. There is a clear and continued need for innovative adherence support programs to optimize viral suppression. To address this gap, we designed and are implementing a randomized controlled trial (RCT) to test the efficacy of the Thrive with Me intervention for MSM living with HIV. Critical components of the protocol are presented.

Objective: The aim of this study is to describe the protocol for rigorously testing the efficacy of Thrive with Me to improve antiretroviral therapy (ART) adherence among HIV-positive MSM residing in New York City.

Methods: A community advisory board and beta testing were used to obtain feedback from HIV-positive MSM on the overall look and feel of Thrive with Me and problems with navigation to finalize intervention components and content. We will enroll 400 HIV-positive MSM residing in the New York City area into a two-arm prospective RCT and follow them for 17 months. Men in the Thrive with Me experimental intervention arm will have access to Thrive with Me for 5 months. Thrive with Me has three primary components: (1) a private social networking feature; (2) tailored HIV and ART adherence information; and (3) medication reminders, self-monitoring, and reflection. Gamification components include badges and leveling up to increase intrinsic motivation to engage with the intervention. Men randomized to the control condition will view a weekly newsletter for 5 months. The newsletter will be delivered via email and contains information on topics related to HIV with the exception of ART adherence. Study assessments will occur at enrollment and 5, 11, and 17 months post enrollment. The primary study outcome is HIV viral load, which is considered an objective indicator of ART adherence.

Results: Participant recruitment for the RCT began in October 2016, and the data collection period is anticipated to end in the Fall of 2019.

Conclusions: The efficacy trial of Thrive with Me will help to fill gaps in understanding about the utility of multicomponent, technology-based interventions to improve ART adherence among HIV-positive MSM. Of importance is the ability for the results

of the Thrive with Me trial to inform best practices for conducting technology-based interventions that incorporate social media features.

Introduction

Background

HIV rates in the United States, for the most recent 5 years data that are available, have declined slightly from 14.2 new HIV diagnoses per 100,000 in 2010 to 12.3 in 2015 [1]. Despite decreases in HIV infection rates among injection drug users, women, and heterosexual men, those attributed to male-to-male sexual contact remain stable. In 2015, 70% of all new HIV infections were attributed to male-to-male sexual contact (including the category of male-to-male sexual contact and injection drug use) [1]. Current US Guidelines for the Use of Antiretroviral Agents [2] state that undetectable viral load (VL) "is one of the most reliable indicators of adherence," which is largely achieved though sufficient and sustained adherence to antiretroviral therapy (ART). Optimal ART adherence reduces excess morbidity and mortality among people living with HIV or AIDS (PLWH) [3] and lowers the probability of forward transmission to sexual partners [4]. However, in a review of studies of the treatment cascade for men who have sex with men (MSM), viral suppression was between 16% and 42% among the 7 reported studies conducted in the United States [5]. The most recent Centers for Disease Control and Prevention (CDC) surveillance data showed that 61% of MSM diagnosed with HIV in 37 states and the District of Columbia had VL below 200 copies/mL [6], although viral suppression is estimated to be lower among all people aware and unaware of their HIV-positive status (49%) [7]. Despite the disproportionate burden of HIV in MSM communities, only three of 13 medication adherence interventions included in CDC's Compendium of Evidence-based Behavioral Interventions include a majority MSM participants; the first is a provider implemented approach evaluated over a decade ago [8], the second is an intensive one-on-one counseling approach [9], and the third is an individual-level, computerized, clinic-based counseling intervention [10]. Thus, advancing tailored and innovative ART adherence interventions for HIV-positive MSM remains a high priority [11].

The use of technology has rapidly grown since 2000, when only 52% of US adults used the internet [12]. Currently, 88% of US adults are online [12], 95% own a cell phone [13], 75% own a smartphone [13], and 68% use Facebook [14]. Technology-based ART adherence approaches have proliferated in recent years [15,16] because of the widespread adoption of technology across sociodemographic groups [12], their ability to reach a broad audience, and their low implementation costs [17]. However,

computerized ART adherence interventions [10,18], including those specifically for MSM [19] and illicit drug users [20], tend to be individually delivered and do not leverage peer-to-peer interactivity that has come to symbolize Web 2.0 [19]. Peer support interventions may facilitate user-generated content through wall or message board posts that create unique social incentives to maintain high engagement in the intervention.

In-person peer support ART adherence interventions have shown moderate success in improving adherence outcomes [21,22]. Simoni and colleagues randomized 224 HIV-positive patients at a public HIV specialty clinic in Seattle, Washington to receive either in-person peer support, pager messaging, both in-person peer support and pager messaging, or usual care [22] for a 3-month period. Assessments occurred every 3 months for a total of 9 months. Participants who received the peer intervention reported higher self-reported adherence at the immediate postintervention assessment, although intervention effects diminished at later assessment periods. Only the pager intervention showed significant effects for improving biological outcomes, suggesting that other adherence supports may be needed to bolster peer support–only interventions.

In response to the growing use of technology and the limitations of in-person ART adherence peer support interventions, we developed and pilot tested the Thrive with Me (TWM) intervention. TWM is a virtual (ie, online) behavioral intervention that includes peer-to-peer communication features, tailored ART and HIV information, and an ART self-monitoring component. TWM is grounded in the information-motivation-behavioral Skills (IMB) model [23,24]. We conducted a pilot study of TWM from February 2010 to April 2010 to assess its feasibility, acceptability, and preliminary efficacy among 123 adult MSM (mean age=43 years; 64.2%, 79/123 white) mostly recruited online in the United States. A full description of the study and its results has been published [25]. Briefly, results showed that 90.2% (111/123) were retained at the final assessment, and there were high acceptability ratings among men assigned to the TWM condition. Although overall adherence scores showed modest improvement from baseline to follow-up among the TWM intervention group compared with the control condition, these differences were not statistically significant. Among MSM who reported recent (<30 days) illicit drug use (16.3%, 20/123 of the sample), those in the TWM condition reported significantly higher overall ART adherence and ART taken correctly with food than those in the control condition.

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Figure 1. Thrive with Me intervention components and the information-motivation-behavioral skills (IMB) model. ART: antiretroviral therapy.
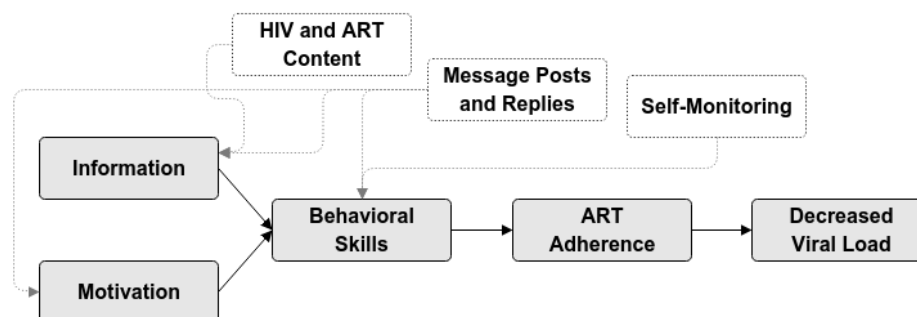
Study Aims

The results of the TWM pilot study suggest that the approach of combining peer support, ART information, and adherence self-monitoring may improve ART adherence among MSM, especially those who use illicit drugs. This paper describes the protocol for a randomized controlled trial (RCT) to assess the efficacy of the TWM intervention to improve ART adherence among adult HIV-positive MSM. The aims of the study were as follows:

> **Primary aim 1:** determine the efficacy of the TWM intervention to increase the proportion of virally suppressed HIV-positive MSM at postintervention time points.
>
> *Hypothesis 1:* a higher proportion of participants in the TWM intervention than control participants will have undetectable VL at postintervention time points.
>
> **Primary aim 2:** assess whether the TWM intervention is more beneficial for HIV-positive MSM who report recent drug use at baseline compared with HIV-positive MSM who do not.
>
> *Hypothesis 2:* recent drug-using participants in the TWM intervention will demonstrate greatest improvements in VL and self-reported ART adherence at postintervention time points compared with nondrug-using participants.

We also propose the following secondary aims:

> **Secondary aim 3:** examine the effects of the TWM intervention on sustained undetectable VL, defined as having an undetectable VL at all postbaseline assessment time points.
>
> **Secondary aim 4:** examine the effects of the TWM intervention on theory-based change process (ie, IMB factors and social support) for improving VL, ART adherence, illicit drug use outcomes, and engagement in HIV care.

Theoretical Basis for Intervention

The IMB model proposes that health behavior change occurs through the provision of relevant information, personal and social motivation to engage in the behavior, and appropriate behavioral skills to enact the behavior [26,27]. The associations between core TWM intervention components (described in detail below) and the IMB model components are shown in Figure 1.

The IMB model has been evaluated and supported using clinic-based samples in Puerto Rico [24], Italy [28], and Mississippi [29]. Using data collected as part of a pilot trial of TWM [30], our team investigated whether the IMB model is a useful predictive model of ART adherence among PLWH who were primarily recruited online and whether the theorized associations between IMB model constructs and adherence persisted in the presence of depression and current drug use [31]. Participants were on average 43 years of age, had been living with HIV for 9 or more years, and mostly male (84.0%, 270/312), white (68.8%, 222/312), and gay-identified (74.8%, 241/312). Using a revised version of the IMB scales, IMB constructs were associated with adherence as predicted by the theory among nondrug users and those with and without depression. However, among drug users, information exerted a direct effect on adherence but was not significantly associated with behavioral skills. These results suggest that the IMB model is an appropriate theoretical foundation for TWM, even when controlling for well-known determinants of adherence disruptions.

Methods

Design

The research activities include a prospective two-arm RCT to test the efficacy of TWM to improve ART adherence among approximately 400 adult gay and bisexual MSM residing in the New York City area (Figure 2). TWM is a multisite study between the University of Minnesota (UMN) in Minneapolis and the Center for HIV Educational Studies and Training (CHEST), which is part of Hunter College, City University of New York. The team in Minnesota, led by principal investigator (PI) Dr Horvath, developed the TWM intervention, scientific protocols, and all training documents for implementation. The team at CHEST, led by coinvestigator Dr Parsons, manages the recruitment, enrollment, and retention of all participants. Following screening and enrollment, participants are randomized to either the experimental (TWM) or control arm. Men in the experimental arm receive access to the TWM intervention for a period of 5 months, whereas those in the control arm receive weekly emails with HIV-relevant content that does not include information about ART adherence. Assessments are conducted in-person at the CHEST offices by trained research personnel and occur for participants in both arms of the study at baseline, 5-month, 11-month, and 17-month follow-up time points. The primary outcome measure for the RCT is VL at the three follow-up assessment time points. We hypothesize that a higher

proportion of participants in the TWM intervention than control participants will have undetectable VL at postintervention time points. We also hypothesize that recent drug-using participants in the TWM intervention will demonstrate greatest improvements in VL and self-reported ART adherence at postintervention time points compared with nondrug-using participants.

As secondary analyses, we will assess whether sustained undetectable VL, defined as having an undetectable VL across all follow-up assessment points, is higher among men in the TWM intervention condition. We will also assess the degree to which self-reported, theoretically derived adherence barriers (information, motivation, and behavioral skills) and social support within and outside the TWM intervention are associated with VL, self-reported ART adherence, illicit drug use outcomes, and engagement in HIV care.

Participants

Men residing in the New York City metropolitan area will be recruited by CHEST staff to participate in this study. New York City was chosen as an ideal location to conduct the study because of the high numbers of HIV-infected MSM residents [1] and since only 38% of residents with HIV are estimated to be virally suppressed [32]. The eligibility criteria are shown in Textbox 1.

Additionally, a 50% target enrollment of drug-using (including powder cocaine, crack cocaine, painkillers, methamphetamine, heroin, hallucinogens, prescription drugs used recreationally, ketamine, MDMA, and poppers) men was established to ensure that both drug-using and nondrug-using men were enrolled in the trial. Due to its common use among HIV-positive and HIV-negative or unknown MSM [33], we did not include users who reported only marijuana use in the drug-using category.

Figure 2. Participants' flow through the Thrive With Me study.
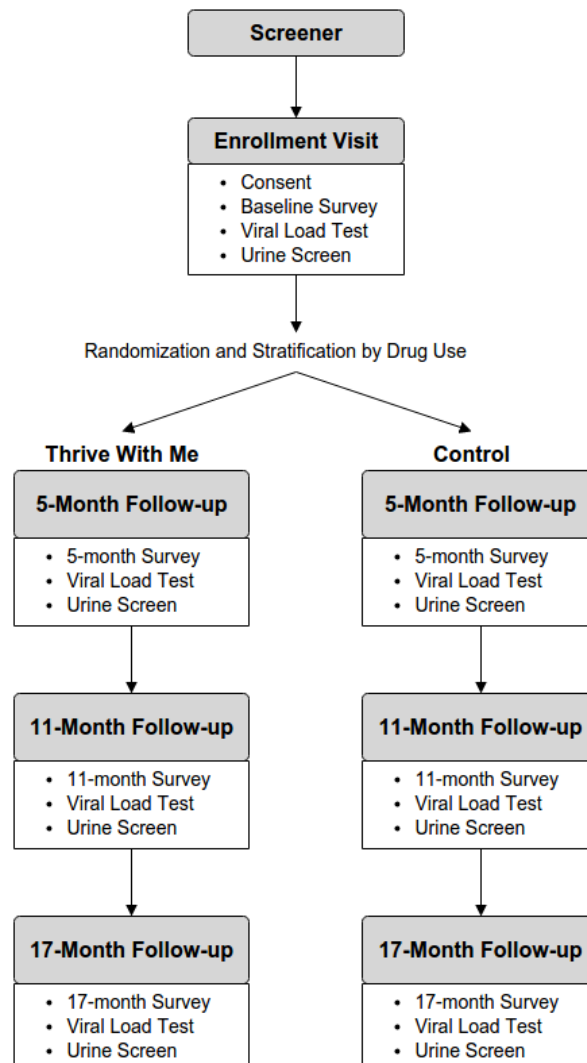
Textbox 1. Eligibility criteria.

Eligibility criteria

- Current male gender

- Having sex with a man in the past year

- HIV-positive serostatus (confirmed by current antiretroviral therapy prescription when possible)

- Reporting a detectable viral load (past year) or potentially suboptimal ART adherence (<90% in the past 30 days)

- English proficiency (as the intervention is in English)

- Residing in the New York City metropolitan area (so that men can attend in-person study visits)

- The ability to send and receive short message service messages

- Having internet access over the active (ie, 5 month) study period

Randomization

Randomization occurs once participants are consented and enrolled in TWM. Participants complete a baseline computer-assisted survey instrument (CASI) programmed using Qualtrics (Provo, UT). At the end of the survey, a research assistant enters a password that enables Qualtrics to randomize the participant to either the experimental or control arm. Randomization was programmed using blocks of 20 (10 intervention and 10 control) to ensure we had enough users in the social network throughout data collection. After randomization, participants are further stratified by recent drug use and nonrecent drug use. Participants are not informed about their assigned arm in terms of intervention or active control, as the arms are described to participants simply as group 1 and group 2.

Recruitment

Participants will be recruited by staff at CHEST, which utilizes both active (eg, direct outreach) and passive (eg, advertising in clinic settings and internet-based) recruitment approaches to effectively recruit HIV+ MSM into intervention trials. CHEST has successfully developed a carefully monitored and organized recruitment structure through both internet- and field-based recruitment efforts. Recruitment efforts involve a preliminary screening process that significantly reduces the number of study-specific screeners conducted by project staff. CHEST uses internet recruitment efforts through online venues that cater to MSM and other populations that are most affected by HIV (eg, Grindr, Scruff, Adam4Adam, Craigslist, Facebook, Instagram, Twitter, and other social media platforms), as well as utilizing email distribution lists and blogs that expand to hard-to-reach populations through connections with nightlife party promoters, sex party promoters, and other community-based leaders or organizations. In addition to internet-based recruitment efforts, CHEST has utilized field-based recruitment strategies in their efforts for reaching HIV-positive MSM from diverse communities, ethnic and racial backgrounds, and sexual identity. Recruiters will conduct on-site preliminary screening via tablets at local bars, clubs, and community events frequented by gay and bisexual men in the New York City area. If a participant is determined to be preliminarily eligible for TWM, they are asked to provide contact information (including name, phone number, and email address) so that a study staff can contact them to perform the full study screener.

During the screening process, participants will be asked if they participated in the beta testing phase of TWM or are currently enrolled in TWM. Responding "yes" to either question will result in ineligibility. Eligible participants' contact information (email, phone number, first and last name) will be automatically cross-referenced with enrolled participant information to capture duplicate participants before baseline and enrollment.

Intervention

Thrive With Me Condition

Several strategies were employed to ensure sustainability, accessibility, and high user acceptance of TWM. To promote sustainability, the software team developed the program on a well-supported, open source, Web development framework and content management system, future-proofing the site against vendor lock-in and providing a platform for delivering a rich feature set within the resource constraints of the project. To promote accessibility, the user experience design team utilized a "responsive Web" approach, wherein the site layout dynamically adapts to suit the size and capability of the user's device (eg, cell phone, tablet, or laptop). This ensured that TWM was available across a variety of devices and eliminated the need for multiple mobile device–specific codebases (eg, native apps). Finally, throughout development, the team sought input from representative users regarding the program interface, features, and design style, increasing the likelihood of high user acceptance upon release.

The active intervention period is 150 days (approximately 5 months). Men in the TWM experimental intervention arm have access to the full TWM website that has three primary components: (1) a private social networking feature (Figure 3); (2) tailored HIV and ART adherence information (Figure 4); and (3) medication reminders, self-monitoring, and reflection (Figure 5). Privacy on the TWM site was prioritized in several ways. First, TWM was designed to be a closed community, such that only participants could gain access to enter the site. Second, because of stigma that HIV-positive MSM commonly face and concerns that some participants may feel uncomfortable disclosing their identities online, we established community rules that men could not post pictures of themselves on the site. Men could choose from a number of avatars that gave them the

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opportunity to tailor their profile without disclosing their identity.

Using asynchronous peer-to-peer interaction, the TWM website was developed to be a safe space for supportive peer-to-peer interactions to promote healthy choices related to living with HIV and medication adherence (Figure 3). Men are encouraged to participate in the TWM social network as much as they are comfortable, similar to other social networking sites. TWM is moderated daily by research staff to identify any posts that appear to reflect self or other harm intentions or behavior, any hostile interactions, or misinformation that is not corrected by group members. TWM staff members post to the feed a few times a week to welcome new members to the site, remind participants of some features of the site, and to announce the winner of a weekly prize drawing for those who are very active on the site.

The TWM website presents HIV-related content to users every day in the form of Thrive Tips (Figure 4). Thrive Tips are content pieces (text, images, videos) that address barriers to medication adherence. There are 300 total Thrive Tips that are released 3 to 4 per day, each tied to an individual item in the IMB ART Adherence Questionnaire (IMB-AAQ; described below). Thrive Tips that reflect a participant's unique ART adherence barrier are shown with a blue triangle in the corner of the tip to indicate to him that the information is particularly relevant to his needs. The longer participants are in the intervention, Thrive Tips are accumulated and stored in an online searchable library. Thrive Tips can be searched by category of information, content recommended for the specific user, content that has been favorited by the user, and tag words. Men retake the IMB-AAQ at the midpoint of the intervention, and all Thrive Tips are displayed again, although reflecting participant's updated adherence barrier profile.

In addition, men receive daily short message service (SMS) reminders to take their medication at a time of their choosing. Men receive follow-up SMS messages asking them to report whether they took their dose that day (or not) and what their current mood is (Figure 5). Once a week, participants are reminded to complete their "weekly check-in," where they are shown their responses to the daily SMS messages and are asked to report on which days in the prior week they used substances (which could include alcohol and drugs). To encourage reflection, men are then prompted to answer a multiple choice question about how their week was overall (ie, "Looking back at your week, how did you handle the tough things you had to do? 1 hot mess; 2 fell on my face; 3 don't stop me now; 4 I will survive; 5 Sasha Fierce") and are given a private text area to record anything from the week that they want to remember. The response options asking men to rate how their week was overall were intended to be engaging to the user, rather than to collect validated data on their perceptions of the quality of their week. Therefore, we did not assess beforehand whether HIV-positive MSM interpreted these items as ordinal. Participants may review past weeks of responses during the active intervention period.

Figure 3. Thrive With Me peer interaction.
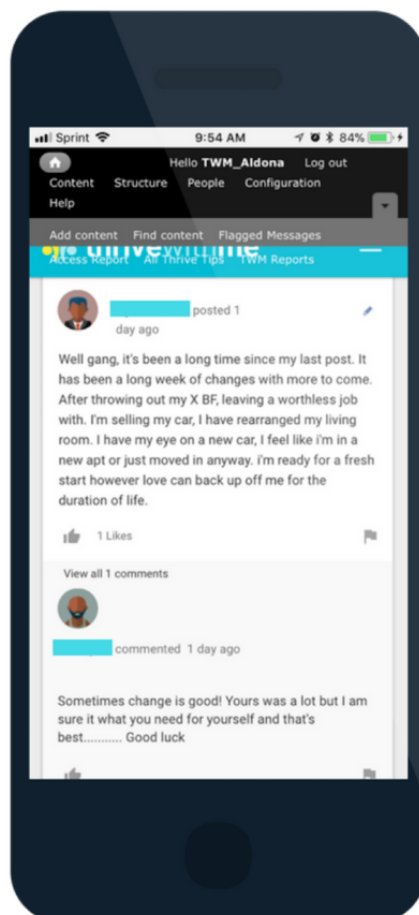
Figure 4. Thrive with Me "Thrive Tip".
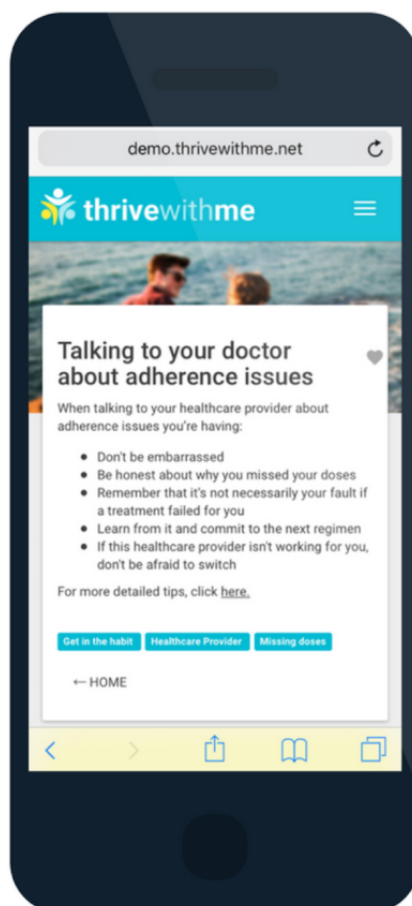
In addition to these three primary components of the TWM intervention, other features of the site include (1) A profile page where men can update their profile and settings, gaming features (eg, points, achievements, and badges; Figure 6); (2) A weekly prize drawing of a US $25 online gift card for those who use the site 5 or more times in the past 10 days; (3) An "About us" page that describes the study and the study team; and (4) A "Getting started" page that provides instructions about how to use the TWM site. Access to the TWM site is given to participants who have the correct username and password and to study staff with the appropriate credentials (Figure 7).

Control Condition

Participants assigned to the control condition receive a weekly email with content similar to a newsletter for 21 consecutive weeks. Each email contains a link with information on a topic related to living with HIV and devoted to improving general well-being but not specifically about ART adherence. Sample topics of the information-only control content include HIV and longevity, HIV and parenting, and HIV and depression. Control content is developed in, and sent from, Qualtrics, to allow for the collection of data on which emails participants open. In addition, at the bottom of each informational page is the question "How would you rate this week's content?" with a 5-star rating from the numeric anchors 1 to 5.

Both the TWM intervention and the control intervention weekly emails are viewable across multiple devices, including smartphone devices, tablet computers, and desktop and laptop computers.

Participant Monitoring and Monitoring Adverse Events

Participant Monitoring

Participants will be informed during the consent process of the "group rules" regarding interactions with one another (eg, "Honesty is important, however, hostile or abusive language will not be tolerated and may be grounds for immediate removal from the study"). These "rules" will also be available with a link on the TWM site. The project coordinator will manually review each day posts that participants write to each other to flag hostile interactions and inaccurate information. Hostile interactions between participants will be handled by, first, reminding the participants in the interaction of the "group rules" regarding appropriate interactions. If the hostility continues, the offending participants will be given a warning that the continued hostility will result in withdrawal from the study if it continues. On the third offense, the offending participant will be withdrawn from the study. Text containing hostile exchanges will be removed from the study website and unavailable to view. In cases in which inaccurate information is found, project staff be guided by exerts on the team to post a comment that provides accurate information on the topic.

Figure 5. Thrive with Me adherence, mood, and substance use self-monitoring.

Monitoring Adverse Events

Study staff will identify adverse events (AEs) and serious adverse events (SAEs) that may occur during the study period. Such events will be immediately brought to the attention of the PI and the investigator team. AEs will be reported to the UMN Institutional Review Board (IRB; 1504S69721) within 5 working days. In the event that the UMN IRB requests follow-up reports regarding an AE, it is the responsibility of the study Pl to submit the report on or before the date requested by the IRB. SAEs will be reported to the UMN IRB and National Institute on Drug Abuse (NIDA) within 72 hours. Subsequent follow-up reports for a specific SAE will be submitted quarterly (ie, every 3 months) to NIDA. The follow-up report on any specific SAE will include correspondence from the IRB as to the determination of whether the SAE was related to the study. In the event that the UMN IRB requests follow-up reports regarding an SAE, it is the responsibility of the Pl to submit the report on or before the date requested by the IRB. The UMN IRB has the authority to suspend or terminate approval of any research at its site that has been associated with unexpected serious harm to participants. The conditions under which the study would be stopped include, but are not limited to, a direct causal link between the study conditions and the hospitalization, impairment, or death of any research participants. Finally, a data safety and monitoring board (DSMB) will be convened to determine safe and effective conduct and recommend conclusion of a trial if significant risks develop or the trial is unlikely to be concluded successfully. The board will consist of three experts in the field of HIV prevention and treatment intervention and will meet yearly.

Preliminary Data

Community Advisory Board

Seven men who had participated in prior research at CHEST and indicated that they wanted to contribute to further research were given contact information for the TWM study site coordinator. Upon expressing interest in serving on a community advisory board (CAB), they were given a brief phone screening to ensure they were male-identified, at least 18 years of age, HIV-positive, currently on ART medications, lived in New York City, English speaking (as materials would all be in English), and had access to the internet. Four members of the CAB identified as African American or black, three identified as white, and two identified as Hispanic or Latino. CAB members were asked to complete three online surveys over the course of 2 months and were compensated US $50 per survey.

Figure 6. Thrive with Me profile and gamification.
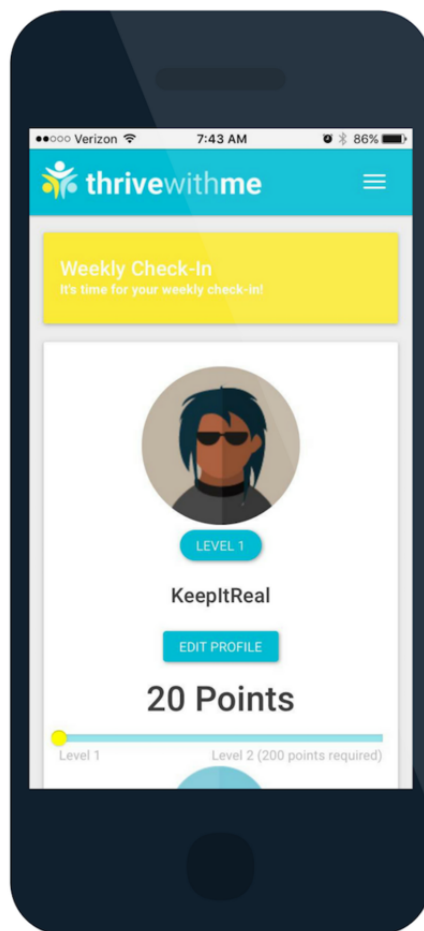
The first CAB survey gathered input on general user experience, particularly aesthetics, language, and usability. For aesthetics, we asked questions about a variety of color palettes and stock photography. Users were asked to rank favorites, given scales of adjective choices to describe aesthetics (ie, traditional vs modern or informal vs formal) and also were given free text options to include other feedback. Language questions were focused on wording of medication reminder SMS text messages, name choices for major features, what words we should use when talking about illicit drugs, and the naming of various badges and achievements. The second CAB survey was used to gather input for HIV-related content that was not directly tied to medication adherence. Suggestions regarding what topics to discuss mostly informed the development of content for the control arm. The third survey solicited feedback on a large assortment of avatar choices for user's profiles, from abstract choices to different portrayals of people. It also included questions about a weekly self-monitoring component to assess clarity, usability, and overall tone of the language.

Beta Testing

A total of 16 men were recruited to beta test the TWM intervention. Beta testing included collecting both usability (ie,

testing for navigation and technical errors) and acceptability (ie, gathering feedback about the intervention features, functions, and design) data. Inclusion criteria were male-identified, living in the NYC metropolitan area, HIV-positive, currently on ART medications, self-reported issues with medication adherence, English-speaking (as the website is in English), access to the internet, able to send and receive SMS messages, and available for follow-up interview.

Eligible men visited CHEST offices in person for two visits during beta testing. During the first visit, men completed a baseline CASI on which a majority of participants identified as non-Hispanic (81%, 13/16) and African American (75%, 12/16). The average age was 36 years. The majority of participants identified as homosexual or gay (94%, 15/16). Participants had been diagnosed with HIV for a mean of 11.6 years. All participants reported a history of lifetime drug use, whereas 13 (81%, 13/16) reported any drug use in the previous 30 days. With respect to ART adherence, participants on average missed 3.7 doses in the past 30 days.

Figure 7. Thrive with Me log-in page.
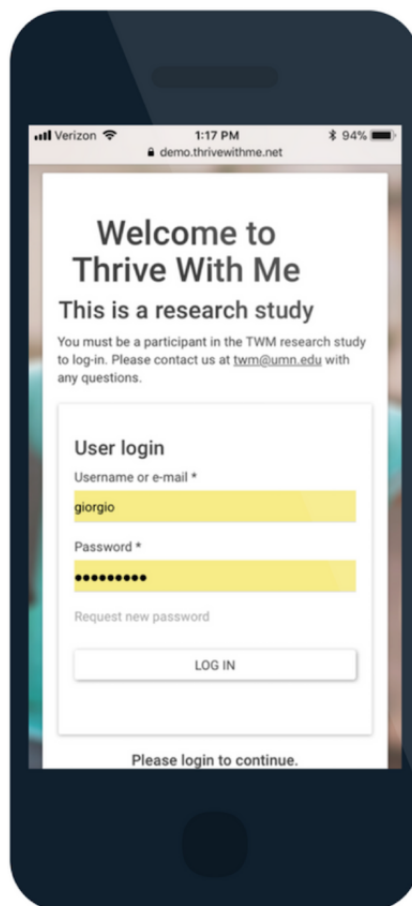
After completing the baseline CASI, participants met individually with staff from CHEST for an orientation to the TWM website. CHEST personnel demonstrated all of the core components of the site from a desktop computer. Participants were also given the opportunity to log in on their mobile phones. Participants were given a "workbook" of tasks to complete on the TWM site over the next 2 weeks and note anything they liked, disliked, problems they encountered, or suggestions for improvement. Participants then scheduled their second visit for approximately 14 days later and were given US $50 for compensation. The first visit typically lasted 90 to 120 min in duration.

During the 2 weeks that men were using the website, research staff from the UMN and CHEST in New York City communicated daily about any technical challenges, participant questions, or other concerns. After 2 weeks of testing the website, participants returned to the offices of CHEST, and staff there facilitated a phone interview between the UMN study coordinator and the participant. The purpose of the call was to gain feedback from participants about problems they encountered as they used TWM, as well as their suggestions for improving the overall look and feel of the intervention. Users were logged into the TWM website during the telephone interview, and participants also had their notes from the workbook if they remembered to bring it with them to the second visit. Interviews typically lasted between 30 to 45 min, and

participants were paid another US $50 to compensate for their time. All 16 participants completed both visits.

Beta testing feedback and how the feedback was incorporated (or not) into the final version of the TWM site is shown in Table 1. Most participants expressed positive opinions about the core features of the site; however, there were several areas in which participants noted opportunities for improvement. Feedback included both content and site design requests, as well as technical issues. Content feedback was incorporated into edits made by the UMN research team, whereas feature requests and technical issues were passed on to site developers. High priority feature requests included changing aspects of the site that were confusing or ungainly, increasing the customizability of users' profiles, and altering the SMS reminder and check-in process. Low-priority feature requests were an orientation to using the site on a smartphone and more personalized options for the site.

Following a final revision of the TWM site based on feedback from beta testing, enrollment into the RCT (Figure 2) began in November 2016.

Outcomes

The study outcomes below are organized as shown in Table 2. Measures are collected using an online survey tool (Qualtrics) at baseline and 5-month, 11-month, and 17-month postbaseline assessment time points. A table of measures administration is shown in Table 2.

Table 1. Participant feedback from beta testing of the Thrive with Me (TWM) site.

Topic	Likes	Dislikes	Participant recommendations	Action taken
SMS[a] reminders	"The med reminders are amazing because they hit on the point, the exact time that I set it for, so it helps so much!...It helps me take my meds every day."	"Sometimes it just says 'bye' at the end of the text message and that's a little brief. Like maybe say something else or don't say anything at all."	New or different options to describe emotions, new valediction	Used more discrete language (multivitamin instead of dose) as default message; Mood responses updated; Changes to greeting messages and discontinued "goodbye" message
Thrive tips	"I think it's amazing...that it gives you tips and like things I didn't even know. I was like that's awesome! I think they're very helpful."			Added Thrive Tips to the first week of the intervention specifically orienting participants to the intervention; Added Thrive Tips to the final 2 weeks of the intervention regarding finding social support after TWM, closure within the intervention and "graduating" from TWM
Mobile features	"On the computer it looked really nice and I liked the layout, like Facebook."	"On the phone, I don't know, it was more difficult to see everything, you had to scroll up and down and left and right and it was just hard to use."	More mobile-friendly design and features, icon on phone's home screen	Updated layout of some Web pages; Added an icon for a phone's home screen and provided participants instructions for setting the icon
Social features	"It was kind of helpful because I read how other people—how they expressed their emotions, how they felt, what they were going through…so it kind of helps you in your day by day so you don't feel like you're alone."	"I wouldn't use it for that. I mean, I don't really want to engage with people who I don't know."	Larger maximum file size for uploads to post on the wall, notification when one's post is commented on or liked	Updated file size to accommodate larger images or graphic interchange formats; Built notification system to track comments and likes within the TWM site (no text, email, or banner notifications were added)
Profile	"Avatar choices are cute, they didn't have faces, they are anonymous, but there should be more choices."	"I don't like the avatars at all. I'm half something and half something else with blue hair…It looks like a muppet."	More diverse options for avatars, profile questions about HIV-related or life-related experiences	Increased avatar choices and added features requested by participants (glasses, afros, more feminine looking options, etc); Added "Talk to me about" feature with "check all that apply" responses for a variety of topics related to HIV and general well-being
Achievements	"They were cute, very cute…They're uplifting, you know, you never know what someone is going through and some people are never told that they do anything right. The badges tell you 'good job'."	"Badges, achievements, I didn't understand it. What are these points? Am I getting money at the end of the day? Why am I doing this?"	More clarity about what earns points and what badges mean	Added a "Getting Started with TWM" Web page to explain all components of the intervention; Updated in-person website orientation to include more details about achievements
Overall	"I mean we walk around with HIV, I have HIV positive friends, but a lot of times the only interaction I would have around HIV positive people would be around sex, so this kind of brings it around, where having that conversation brings it out of the sexual realm and maybe more into the supportive realm, for people who may not have that already."	"For people newly diagnosed or early in their diagnosis this would be a very very useful tool…but for me personally it's just not practical. I don't need the things that it offers."	N/A[b]	N/A

[a]SMS: short message service.

[b]N/A: not applicable.

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Table 2. Schedule of measures administration. An "X" indicates that the measure was assessed at the corresponding time point. A "—" indicates that the measure was not assessed at the corresponding time point.

Variable	Measures	Assessment period			
		Baseline	5-month follow-up	11-month follow-up	17-month follow-up
Primary outcome					
Viral load (VL)	Undetectable=VL<20 copies/mL	X	X	X	X
Demographics and HIV history					
Age	Age in years	X	—	—	—
Race or ethnicity	Race, ethnicity (Hispanic or Latino)	X	—	—	—
Sexual orientation	Sexual orientation	X	X	X	X
Education	Highest level of education completed	X	X	X	X
Employment	Employment status, student status	X	X	X	X
Income	Household income, number dependents on income	X	X	X	X
Community	Population of residence	X	X	X	X
Health insurance	Type of health care coverage	X	X	X	X
Medical or clinical variables					
Self-reported HIV history	Year and month diagnosed with HIV, AIDS diagnosis	X	—	—	—
Self-reported ART[a] adherence					
Prescriptions	Number of prescribed medications, vitamins, and supplements	X	X	X	X
Antiretroviral medications	Year started HIV medications, HIV medications currently taken, number of doses per day	X	X	X	X
Adherence	Doses missed (past 4 days, 30 days), % adherence (past 30 days), % taken within 2 hours of scheduled dose (past 30 days), how good a job in taking HIV medications, challenges to adherence	X	X	X	X
Prior adherence services	Previous adherence-related information or services received	X	X	X	X
IMB[b]-ART Adherence Questionnaire					
Information	ART adherence information	X	X	X	X
Motivation	ART adherence motivation	X	X	X	X
Behavioral skills	ART adherence behavioral skills	X	X	X	X
Engagement in HIV care					
Appointments	Last HIV care appointment, appointments scheduled and missed (past 6 and 12 months), upcoming appointment scheduled	—	—	X	X
Engagement	Patient Activation Measure	—	—	X	X
Substance use					
Urinalysis	Cocaine, methamphetamines, marijuana, and opiates	X	X	X	X
Alcohol	Alcohol Use Disorders Identification Test	X	X	X	X
Drug use	Drug use (lifetime) and frequency (past 30 days) of 14 illicit drugs (or other), ever sought help or treatment for alcohol or drugs	X	X	X	X
Psychosocial risk factors					
Depression	Center for Epidemiological Studies-Depression 10-item scale measuring depressive symptoms in past week	X	X	X	X
Stress	Perceived stress in past 30 days	X	X	X	X

Variable	Measures	Assessment period			
		Baseline	5-month follow-up	11-month follow-up	17-month follow-up
BSSS-4[c]	BSSS-4	X	X	X	X
Life chaos	Measure of Life Chaos	X	X	X	X
HIV stigma	HIV Stigma Scale (internalized, anticipated, enacted)	X	X	X	X
Resiliency	HIV resilience items	X	X	X	X
Relationship and sexual risk					
Relationship	Relationship status, relationship sexual agreement	X	X	X	X
General sex	Number of sexual partners by gender (past 3 months)	X	X	X	X
MSM[d]-specific sex	Male sexual contacts, frequency of anal sex and condom-less anal sex; condomless anal sex by partner serostatus, partner pre-exposure prophylaxis use (past 3 months)	X	X	X	X
Social support					
Social support	MOS[e]	X	X	X	X
TWM[f]-specific social support	Emotional or information support from MOS, Social Support Questionnaire 6 within TWM	—	X	—	—
Technology use					
Overall technology	Social media use, mobile phone use, service provider, device ownership, internet access	X	X	X	X
TWM navigation and use					
TWM navigation	System Usability Scale, reasons for using TWM	—	X	—	—
User engagement	Data captured while participants interact with TWM	X	X	X	X

[a]ART: antiretroviral therapy.

[b]IMB: information-motivation-behavioral skills.

[c]BSSS-4: Brief Sensation Seeking Scale-4.

[d]MSM: men who have sex with men.

[e]MOS: Medical Outcomes Study.

[f]TWM: Thrive with Me.

Primary Outcome

Blood draws will be taken to assess the effects of the *TWM* intervention on VL, one of the most objective and reliable indicators of ART adherence [2]. Blood will be drawn by a certified phlebotomist and analyzed by Quest Diagnostics. Plasma VL is considered undetectable at <20 copies/mL. Results of VL testing is provided to participants upon request.

Demographic and HIV History

Common demographic factors will be collected, including gender, age, race or ethnicity, sexual activity with men, income, educational attainment, employment status, and current health insurance. Self-reported HIV history factors include the year and month the participant first tested positive and whether or not they have ever received an AIDS diagnosis.

Self-Reported Antiretroviral Therapy Adherence

Participants are asked to report the medication they are currently taking, the total number of HIV medications taken, and the number of doses of HIV medication taken each day. Next, items adapted from Adult AIDS Clinical Trials Group [34] and from a more recent study by Wilson and colleagues assessing the validity of an ART adherence scale [35] are used to assess aspects of self-reported ART adherence. Items include the number of dosses missed in the past 4 days and in the past 30 days, how "good of a job" participants believed they are doing in taking their HIV medications in the way they are supposed to (from "very poor" to "excellent"), a visual analog scale to assess the percentage of HIV medications taken in the past 30 days and the percentage of HIV medications taken within 2 hours of the correct time in the past 30 days (both scales in 10 percent increments from 0 to 100), and what types of ART adherence support services they are currently receiving at their clinic.

To assess theoretically derived ART adherence strengths and barriers, IMB-AAQ [36] will be completed by participants, as it was in the TWM pilot trial [30,37], and by other research teams [18,30]. The IMB-AAQ is a 33-items measure that assesses adherence-related information (9 items), personal and social motivation (10 items), and behavioral skills (14 items) on a 1 to 5 Likert scale. Responses to these items will be used to tailor the presentation of the Thrive Tips to participants as described earlier.

Self-Reported Engagement in HIV Care

At the 11-month and 17-month assessment, participants will be asked to report the number of health care appointments for HIV they scheduled and missed in the past 6 months and past 12 months, how many months ago they most recently missed an appointment, and whether they have an HIV health care appointment scheduled in the next 6 months. The 13-item Patient Activation Measure [38] will be used to assess patient knowledge, skill, and confidence for self-management of their health care. The pattern of HIV care attendance and participants' beliefs about the self-management of their health care will be used to characterize their engagement in HIV care.

Substance Use and Mental Health Variables

Substance use will be assessed in two ways. First, men will take urine screens at each assessment time point to assess for the following illicit substances: cocaine, methamphetamines, marijuana, opiates, and phencyclidine, using the Integrated E-Z Split Key Cup II-5 panel (Innovacon Laboratories). This test is capable of detecting drugs from 1 to 4 days after use, except for chronic marijuana use, which can be detected for up to 30 days [39]. Second, using items adapted from the TWM pilot study [30], lifetime and recent (past 6 months) use of the following illicit drugs will be assessed: marijuana, poppers (amyl nitrate), pain pills purchased on the street (oxycontin; percocet), powder cocaine, crack cocaine, amphetamine, methamphetamine, ketamine, ecstasy, heroin, cocaine and heroin mixed together, and hallucinogens. Participants also have the option to write in a drug not on the list. If a participant reported taking an illicit drug(s) in the past 6 months, he was asked to write in the number of times he used that drug(s) in the past 30 days. The Alcohol Use Disorders Identification Test (10-item alcohol abuse scale) is used to assess problematic alcohol use [40,41].

We will assess a broad range of mental health factors associated with ART adherence using widely used and validated standardized scales, including the Center for Epidemiological Studies-Depression (10-item depression scale) [42], the Perceived Stress Scale (14-items) [43], the 4-item Brief Sensation Seeking Scale [44], the 6-item Life Chaos Scale [45], and the HIV Stigma Scale [46]. In addition, 10 items from a HIV Resiliency Scale is used to assess the ability to cope with difficult life circumstances and positive beliefs about the self [47].

Relationship and Sexual Risk

We will assess each participant's current relationship status (eg, "I am legally married" and "I am single and having sex with others") and, if the participant reports being in a relationship, what agreement the participant has with his partner about sex outside the relationship (eg, "Both of us have sex with other separately" and "I have sex with others, but don't know about my partner") from items used in a prior study by members of the research team [48]. Next, we ask men to report the number of sexual partners they had in the past 3 months, who were male, female, and transgender (male and female separately). Finally, for participants' male sex partners, we ask them to report the number of sexual contacts with men; the frequency of anal sex

and anal sex without a condom; condomless anal sex acts with HIV-negative, HIV unknown, and HIV-positive partners; and the number of condomless sex acts with HIV-negative partners where the partner was on preexposure prophylaxis.

Social Support Variables

Two scales will be used to assess social support outside of and inside the TWM intervention. First, the *Medical Outcomes Study (MOS) Social Support Survey* (or *MOS*) is a validated 19-item instrument [49] that assesses the availability of four types of social support: emotional or informational, affectionate, tangible, and positive social interaction on a 1 (none of the time) to 5 (all of the time) scale. We will ask participants to complete the MOS at all time points to assess general social support. Additionally, we will use the 8-item emotional or informational support subscale (eg, "Someone to turn to for suggestions about how to deal with a personal problem") to assess social support within the TWM intervention at the 5-month follow-up survey. Second, the *Social Support Questionnaire 6* [50] will be used to assess *who* provides support to whom in TWM and participants' overall *satisfaction* with that support. Participants in the *TWM* intervention arm will be asked to indicate whether they received six types of specific support (eg, Whom can you really count on in the TWM study to help you feel more relaxed when you are under pressure or tense?). If the participant stated that he received a specific type of support, he is asked to report the username(s) of other participants in TWM who provided that type of support. Finally, men will be asked their overall satisfaction with the support they received during their time in TWM on a 6-point scale, from very dissatisfied (1) to very satisfied (6).

Technology Adoption and Use

Technology use questions and items assessing participants' attitudes toward technology were taken from items developed by the Pew Research Center [51]. Men in TWM will report whether and how frequently they use social networking service (eg, Facebook and Instagram), what type of mobile phone they use, their service provider, the average number of SMS (ie, text) messages they send and receive in a month (with categorical response options), whether they own a desktop or laptop computer or a tablet computer, and where they access the internet. To assess how men in the study use their mobile phones, they are asked to state whether they have used their mobile phone for twelve activities (eg, looked up information about a health condition or reserve a taxi or car service).

Ease of Use of the Thrive With Me Intervention

Men randomized to the TWM intervention arm will be asked to rate ease-of-use of the TWM using the System Usability Scale (SUS) [52]. The SUS is a 10-item measure that asks men to rate on a 1 (strongly disagree) to 5 (strongly agree) scale how much they agree with statements about the ease with which they were able to navigate TWM (eg, "I found Thrive With Me unnecessarily complex" and "I found the various functions in Thrive with Me to be very well integrated"). Men in the control condition were not asked these items as they only received weekly emails.

User Engagement

Intervention use data will be collected during the active trial period to assess user engagement with the intervention. Intervention use data will include the following variables reflecting peer-to-peer interaction: (1) date of post, (2) original post content, (3) subject identity document (ID) of original post, (4) content of replies to the original post, and (5) subject ID of each reply. Additional user engagement variables collected are (1) Frequency of wall posts by subject ID, (2) Number of comments by subject ID, (3) Number of Thrive Tips viewed, (4) Number of recommended Thrive Tips viewed, (5) Number of responses to SMS medication reminders, (6) Number of mood responses reported, (7) Number of weekly check-ins completed, (8) Total number of active days, (9) Total points earned, and (10) Total badges earned (as well as which badges earned by participant ID).

Statistical Analysis

Analyses will be performed using Stata or SE v13 or later. The study design is a 2 (condition: intervention vs control) X 4 (time: baseline, 5, 11, and 17 months) randomized trial, with condition a between-subjects effect and time a within-subjects effect. The two primary outcomes are dichotomous: undetectable VL (undetectable=VL <20 copies/mL vs detectable=VL >20 copies/mL) and adherence to ART (high adherence ≥90% adherence vs low adherence <90% adherence). Mixed-effect logistic regression models will be used to test hypotheses. These models will include main effects for condition and time and the condition × time interaction (a 3 degree of freedom comparison; the overall test of the hypothesis). We will also estimate a series of single degree-of-freedom comparisons (using planned contrasts) to estimate the effect of the intervention on adherence at the three postintervention follow-ups relative to baseline. We will primarily estimate effects as intention to treat. Efficacy of the *TWM* intervention will be indicated by a statistically discernable improvement in ART adherence and VL at 17 months.

To investigate whether there is greater benefit from the *TWM* intervention for drug-using participants compared with nondrug-using participants, we will use the approach described above with the two additional factors—self-reported current (past 5 months) drug use and the interaction with intervention (and time). In a similar manner, we will conduct exploratory analyses to identify other baseline participant risk groups for which the intervention is most beneficial. In addition, for participants in the *TWM* intervention, we will examine the effect of type and amount of intervention exposure (ie, which component usage are related to outcomes) on improvement in ART adherence.

Incentives

Participants are paid US $50 in cash at the end of every in-person visit (baseline and 5-month, 11-month, 17-month assessments). Participants in the intervention group also are eligible to win a weekly prize drawing of a US $25 electronic gift card. Only active users who complete actions on the TWM site for 5 out of 10 days are eligible for the weekly prize drawing.

Sample Size and Power Calculation

TWM will be tested in a two-arm RCT with a target N of 400 participants split equally between the intervention and control groups. Using variance and effect size estimates from the pilot study, power calculations determine that this sample size will allow for an 11 percentage point detectable difference in undetectable VL between intervention and control (eg, 71% undetectable vs 60% undetectable) at any of the three postintervention follow-up assessments relative to baseline (tested using planned contrasts described above). Detectable differences are similar for adherence and other secondary outcomes.

Ethics Statement

All study procedures have been approved by the UMN IRB and Hunter College City University of New York Internal Review Board. One IRB does not cede to the other, and investigators from each institution report to their respective IRB.

A Certificate of Confidentiality has been obtained from the NIDA. Additionally, a DSMB has been established to provide regular oversight of research practices and activities to protect human subjects and the integrity of the data in the study. The DSMB comprised independent experts in the fields of HIV-positive populations, technology-based interventions, RCT methodology, and social support interventions. The study is registered on the national registry of clinical trials at clinicaltrials.gov; trial number NCT02704208.

Results

The TWM RCT was launched in October 2016 and is ongoing. Baseline enrollment was completed in April 2018. Follow-up assessments will continue through August 2019.

Discussion

Adherence to HIV medication continues to be problematic, with only 58% of HIV-positive persons aged 13 years or older in 37 states and the District of Columbia virally suppressed according to the latest surveillance report from the US CDC [6]. Suboptimal ART adherence is the result of a complex interplay between individual-, social-, societal-, and cultural-level factors, and primary reasons for missed doses can vary by sociodemographic dimensions [53-56]. Therefore, theoretically grounded behavioral interventions are needed to address these complex reasons for nonadherence among at-risk groups. However, in-person ART adherence interventions are often costly and require highly trained personnel to deliver intervention components. The TWM intervention leverages current mobile technologies (ie, a dynamic online website and SMS text messaging), as well as Web 2.0 technologies that allow users to generate and share content with each other [57], to impact ART adherence among drug-using and nondrug using MSM. Results of this efficacy trial would advance ART adherence science by providing evidence for this approach and, if effective, could inform subsequent interventions that also use either existing (eg, Facebook) or new social media platforms.

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Technology-based behavioral interventions that use peer interactions to promote support have the potential to be highly engaging and use social motivation to create behavior change. However, there is limited knowledge on how to conduct these and other types of social media interventions. Important questions include (1) Is it more effective to use an existing social media platform (eg, Facebook) for intervention or develop a private virtual community? (2) What is the optimal way to monitor and manage activity within the community? (3) How do we engage users with each other in virtual communities? (4) What other features or components are needed to supplement the community feed to maximize benefit? And (5) When do we bring users into a virtual community (eg, immediately after being diagnosed with HIV or only after several months of adapting to their new diagnosis) and how frequently should users engage in them (ie, should they continuously be engaged or can users come in and out of the virtual community as needed) to be most effective? These and other questions about the use of virtual social support and other types of social media interventions will require a sustained research effort to answer. The lessons learned from the TWM study will begin to provide some answers to these questions to advance intervention science in this emerging area.

Acknowledgments

Conflicts of Interest

None declared.

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Abbreviations

AE: adverse event
ART: antiretroviral therapy
CAB: community advisory board
CASI: computer-assisted survey instrument
CDC: Centers for Disease Control and Prevention
CHEST: Center for HIV Educational Studies and Training
DSMB: data safety and monitoring board
IMB: information-motivation-behavioral skills
IRB: institutional review board
MOS: Medical Outcomes Study
MSM: men who have sex with men
NIDA: National Institute on Drug Abuse
PI: principal investigator
PLWH: people living with HIV or AIDS
RCT: randomized controlled trial
SAE: serious adverse event
SMS: short message service
SUS: System Usability Scale
TWM: Thrive with Me
UMN: University of Minnesota
VL: viral load

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<u>Protocol</u>

A Challenge-Based Approach to Body Weight–Supported Treadmill Training Poststroke: Protocol for a Randomized Controlled Trial

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Abstract

Background: Body weight support treadmill training protocols in conjunction with other modalities are commonly used to improve poststroke balance and walking function. However, typical body weight support paradigms tend to use consistently stable balance conditions, often with handrail support and or manual assistance.

Objective: In this paper, we describe our study protocol, which involved 2 unique body weight support treadmill training paradigms of similar training intensity that integrated dynamic balance challenges to help improve ambulatory function post stroke. The first paradigm emphasized walking without any handrails or manual assistance, that is, hands-free walking, and served as the control group, whereas the second paradigm incorporated practicing 9 essential challenging mobility skills, akin to environmental barriers encountered during community ambulation along with hands-free walking (ie hands-free + challenge walking).

Methods: We recruited individuals with chronic poststroke hemiparesis and randomized them to either group. Participants trained for 6 weeks on a self-driven, robotic treadmill interface that provided body weight support and a safe gait-training environment. We assessed participants at pre-, mid- and post 6 weeks of intervention-training, with a 6-month follow-up. We hypothesized greater walking improvements in the hands-free + challenge walking group following training because of increased practice opportunity of essential mobility skills along with hands-free walking.

Results: We assessed 77 individuals with chronic hemiparesis, and enrolled and randomized 30 individuals poststroke for our study (hands-free group=19 and hands-free + challenge walking group=20) from June 2012 to January 2015. Data collection along with 6-month follow-up continued until January 2016. Our primary outcome measure is change in comfortable walking speed from pre to post intervention for each group. We will also assess feasibility, adherence, postintervention efficacy, and changes in various exploratory secondary outcome measures. Additionally, we will also assess participant responses to a study survey, conducted at the end of training week, to gauge each group's training experiences.

Conclusions: Our treadmill training paradigms, and study protocol represent advances in standardized approaches to selecting body weight support levels without the necessity for using handrails or manual assistance, while progressively providing dynamic challenges for improving poststroke ambulatory function during rehabilitation.

Trial Registration: ClinicalTrials.gov NCT02787759; https://clinicaltrials.gov/ct2/show/NCT02787759 (Archived by Webcite at http://www.webcitation.org/6yJZCrIea)

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Introduction

Background

Stroke continues to remain the leading cause of long-term neurological disability in the United States [1]. Although there is heterogeneity in the severity and level of disability post stroke, greater than 80% of all stroke survivors are likely to experience walking deficits due to hemiparesis [2]. Altered hemiparetic motor control causes balance and gait impairments, which result in asymmetric, slow (ie, 0.1 to 0.8 m/s), and inefficient walking patterns [3-5]. Such walking patterns place stroke survivors at a greater fall risk, with ambulatory stroke survivors being twice as likely to experience falls compared with elderly individuals [6,7]. Fear of falling, along with generalized deconditioning, comorbidity burden, and lack of social support and self-confidence, confines stroke survivors to sedentary lifestyles [8]. Such lifestyles limit participation in daily activities and predispose stroke survivors to secondary health conditions that negatively impact their overall quality of life [9].

Treadmill Based Locomotor Interventions for Poststroke Rehabilitation

Not surprisingly, improving walking function is the most common rehabilitation goal stated by the majority of stroke survivors [10]. Unfortunately, most gait rehabilitation paradigms are limited in their ability to generate transferable training gains, to help improve poststroke community ambulatory function [11]. To promote motor learning and activity-dependent neuroplasticity changes during rehabilitation, increased practice of locomotor skills in different situational contexts is required [12]. However, various factors have been shown to limit context-based task practice and transferable training gains during rehabilitation, such as decreased active participation, low cardiovascular training intensities, lack of dynamic balance challenges, over-reliance on clinician manual assistance, and lack of opportunities for prolonged practice of skills applicable to real-world community ambulation [13,14]. To collectively address these factors and to promote greater opportunity for motor learning during gait rehabilitation, several studies recommend treadmill-based gait training paradigms [15], including the recent American Heart Association (AHA) scientific report for exercise training in stroke survivors [16]. However, most treadmill paradigms, especially those that integrate limb unweighting via body weight support (BWS), have had varying degrees of success over the past few decades, with some studies reporting no significant outcome differences compared with over-ground training approaches [17,18].

Need for Challenge-Based Body Weight Support Treadmill Training Post Stroke

Most BWS treadmill paradigms also tend to use external supports (ie, safety harnesses, handrails) and/or therapist- or robot-guided movements that may limit stroke survivors from independently training at desired exercise intensities and/or the ability to challenge their dynamic balance [13,19]. In addition, the lack of context in providing training challenges to help balance confidence and walking independence for navigating through common real-world obstacles further limits training gains [20,21]. Given the variability of results with BWS treadmill training, a recent Cochrane review calls for further investigation of BWS training outcomes using task-specific paradigms of greater training intensities, without handrail support in ambulatory stroke survivors [22]. Unfortunately, safety concerns and limitations in technology restrict most BWS paradigms in their ability to provide challenging yet safe dynamic balance tasks, while training at higher intensities to help stroke survivors overcome their fear of falling and improve their walking function [16,23].

Thus, the purpose of our study was to examine 2 unique intent-driven, BWS treadmill training paradigms, of similar cardiovascular intensity that emphasizes different dynamic walking challenges encountered during community ambulation. The first paradigm involved walking without any handrail support or manual assistance (ie, hands-free [HF] walking [control group]), whereas the second paradigm incorporated practicing 9 essential challenging (C) mobility skills along with HF walking (ie, HF+C walking), relevant for navigation through common environmental obstacles/hazards. We designed both paradigms based on current neurorehabilitation [14] and AHA exercise recommendations for stroke survivors [16]. We used a novel, robotic, intent-driven, treadmill walking system [24] to provide BWS and a safe gait training environment for both groups. We were primarily interested in assessing the feasibility and impact of both treadmill training paradigms on poststroke walking performance and community ambulation capacity, respectively. We hypothesized that the HF+C group would demonstrate greater balance and functional gait improvements compared with the HF group due to increased practice opportunity of essential challenging mobility skills [25] along with HF walking.

Methods

Study Design

We conducted a 6-week, single-blinded, randomized, and parallel-arm study to examine the effects of 2 intent-driven, BWS treadmill training intervention groups (ie, HF training, and challenge (C) with HF (HF+C) training), on improving balance and functional walking outcomes in community-dwelling chronic stroke survivors, with mild-to-moderate hemiparetic gait impairments.

Sample Size Estimation and Group Allocation

We used a single-factor repeated measures analysis of covariance (ANCOVA; ie, initial walking speed as a covariate) at 80% power, 2-tail level of significance of .05 (ie, $P<.05$), and an effect size of 0.4 for a gait velocity difference of 0.16 m/s (ie, minimally clinically important difference), to determine

our sample size for each group. Our estimated sample size was 16 individuals per group; however, we aimed to recruit 20 participants in each group to account for attrition. Thus, our goal was to recruit a total of 40 individuals with poststroke hemiparesis, over a period of 3 years.

Study Center

We conducted all study meetings, participant assessments, and training sessions at the University of Alabama at Birmingham (UAB) Locomotor Control and Rehabilitation Robotics Laboratory (Locolab).

Ethics and Recruitment

We obtained study approval from the UAB Institutional Review Board (IRB protocol no: F120425008). The LocoLab program

coordinator recruited study participants from the greater Birmingham area, using the UAB Stroke Registry list and an initial phone-screening form (Multimedia Appendix 1). Screened participants and their caregiver (if necessary) met with the program coordinator, who explained the study protocol in detail. Participants who provided informed consent were then scheduled for their baseline assessments.

Initial Screening

An experienced physical therapist, blinded to the training interventions, evaluated all consented participants using our study inclusion or exclusion criteria to approve participants for study enrollment (Textboxes 1 and 2).

Textbox 1. Study inclusion criteria.

1. Age 19 years and above, community-dwelling, unilateral stroke survivors

2. History of cerebrovascular accident (ie, ischemic or hemorrhagic) confirmed by computed tomography, magnetic resonance imaging, or clinical criteria

3. At least 5 months after stroke incident

4. Able to ambulate at least 14 m with/without an assistive device or the assistance of one person, with a self-selected comfortable walking speed of ≤1.0 m/s

5. Able to demonstrate receptive and expressive communication ability.

6. Primary care physician approval for exercise (obtained via the Health Insurance Portability and Accountability Act, that is, HIPPA-approved guidelines)

7. Willing to provide voluntary informed consent

Textbox 2. Study exclusion criteria.

1. Presence of serious or uncontrolled cardiovascular conditions

   - Resting systolic blood pressure >180 mm Hg

   - Resting diastolic blood pressure >110 mm Hg

   - Resting heart rate >100 bpm

   - History of uncontrolled arrhythmias/angina/syncope

2. Presence of amputations and/or any severe musculoskeletal problems that restrict walking, for example:

   - Recent fractures of the lower limb

   - Open wounds/abscess

3. Use of spasticity management drug therapies for affected lower limb before participation, for example:

   - Botulinum toxin injection (<4 months earlier)

   - Phenol block injection (<12 months earlier)

   - Intrathecal baclofen or oral baclofen (within the past 30 days)

4. Any cognition involvement impairing ability to follow instructions and/or Mini-Mental State Exam Score <24

5. Past participation in any study examining the effects of long-term body weight support treadmill training in (>4 weeks of training); limb-loaded pedaling or lower extremity strengthening; or enrolled in any ongoing study that evaluates lower extremity function

6. Participant was unable to arrange for transportation to the study site for all evaluations and intervention sessions

7. Participant planned to move out of the area within 18 from the time of study enrollment

Randomization and Stratification

We randomized participants to each of the 2 training groups (HF or HF+C) and aimed for a 1:1 allocation ratio to minimize bias and group confounding. We also stratified participants within each group, based on their self-selected over-ground comfortable walking speed (CWS) as having mild (initial CWS<0.5 m/s) or severe (initial CWS≥0.5 m/s) locomotor impairment, using the walking speed classification by Perry et al [26] (Figure 1). We used a random number generator website [27] to generate 2 lists, of 0 and 1 sequences. We assigned participants in group 0 to the HF group and participants in group 1 to the HF+C group, using an open-ended block randomization scheme. The principal investigator (PI) assigned participants to either training group. The program coordinator gave participants their group assignment in opaque envelopes and sequentially enrolled and scheduled all training sessions and assessments, for each participant, for the duration of the study. We also blinded participants to their intervention outcomes.

## Robotic Treadmill Interface for Hands-Free Gait Training in Both Groups

Both groups trained on a novel robotic treadmill interface, which consists of a robotic-assistive device, called the KineAssist (KA;

HDT Robotics, Salon Ohio, US) [28,29], synced to a Bertec treadmill [30]. The KA has been used in various studies to investigate both poststroke and nonimpaired walking biomechanics under different conditions [28,30-33]. The KA interacts with an individual walking inside it through a pelvic harness that secures their hips and waist through flexible cloth straps (Figure 2). The pelvic harness is attached to the KA's pelvic mechanism that rests at the height of the individual's center of mass (COM) and can provide vertical BWS (for a maximum body weight of 350 pounds and maximum height of 6 feet 5 inches). Two bidirectional force transducers at each hip enable the mechanism to sense drops in height and essentially *catch* the individual in the event of a misstep or loss of balance. This feature provides a safe environment and prevents falls during training. In addition, the force transducers and treadmill belt are paired through software to form a "force-velocity relationship"; the transducers sense the net force applied to the pelvic mechanism and send a signal to move the treadmill belt, making it an intent-driven treadmill. Thus, an individual walking inside the interface can control the speed of the treadmill and walk at their self-selected CWS (ie, intent-driven), with or without varying levels of BWS.

Figure 1. Study-flow for both paradigms from initial screening, randomization, and stratification to training (6 weeks) with follow-up at 6-months. *CWS: comfortable walking speed.
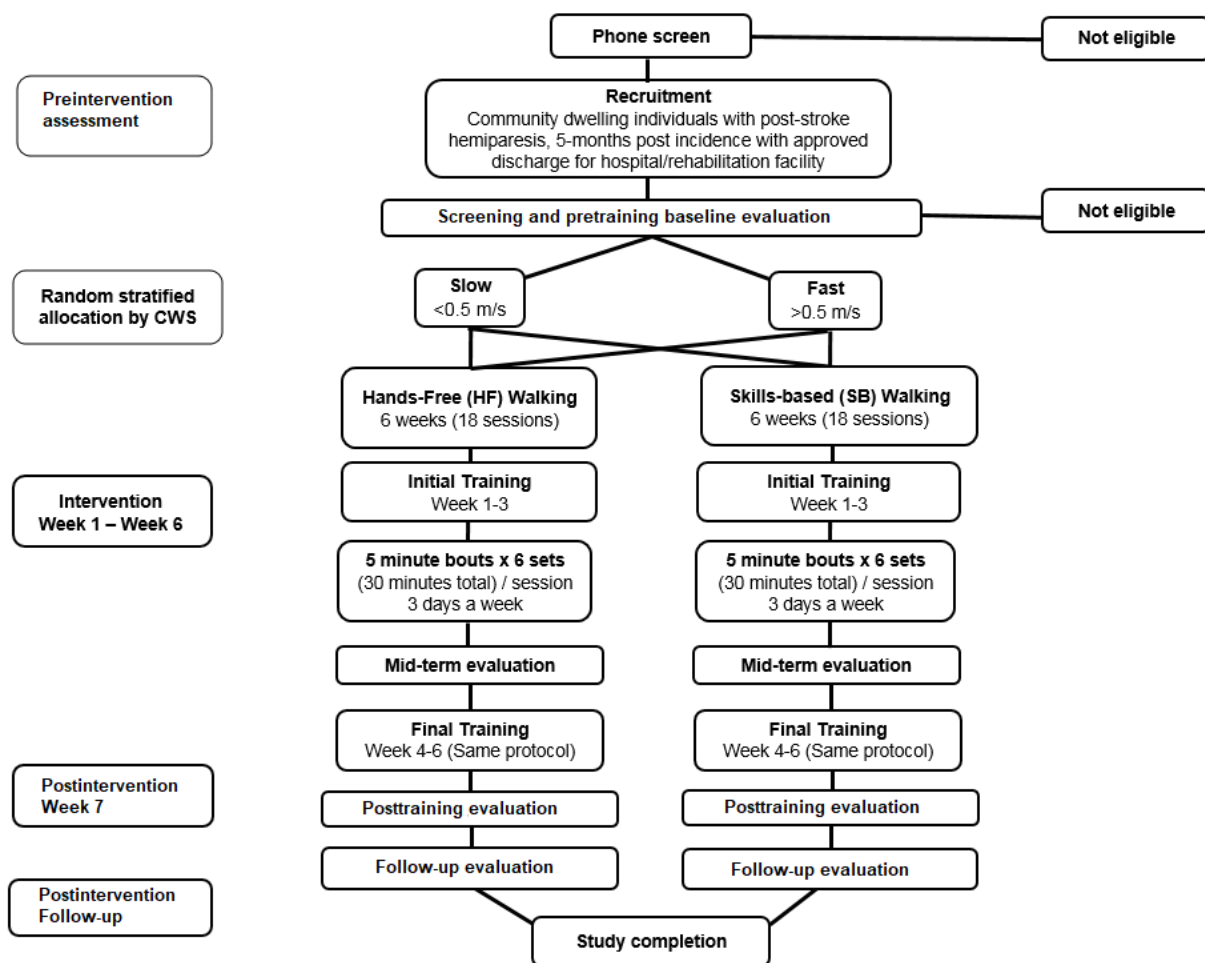
Figure 2. Individual poststroke walking in the KineAssist (KA) treadmill interface. The KA interface consists of a pelvic mechanism with 2 bidirectional force transducers and 2 interactive force rings attached to a pelvic harness and synced to Bertec treadmill.
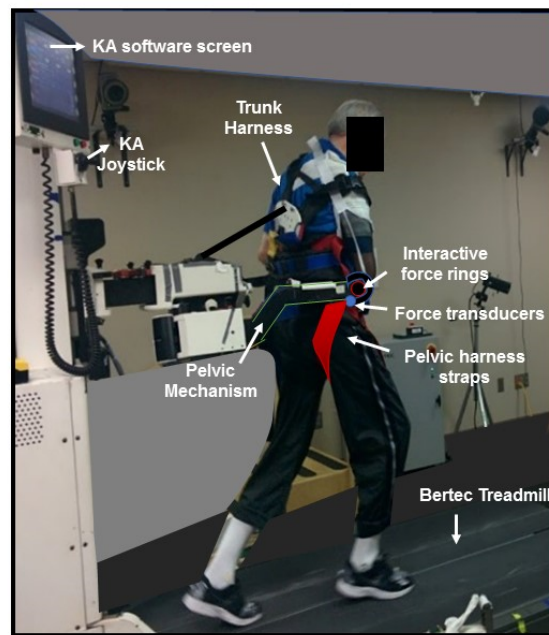
Unlike nonrobotic environments that use motorized treadmills combined with overhead BWS harness systems, with or without handrails/external support [17,34,35], the KA interface eliminates reliance on any external support and offers the user control over their own gait speed through the intent-driven treadmill. When the *safety-catch* feature is triggered, force rings on either arm of the pelvic mechanism (see Figure 2) allow the researcher/therapist to interactively assist the individual back to a standing position by amplifying applied forces to each ring in the vertical direction. Thus, participants learn to address their falls and stumbles inside the interface as "errors" that they can then learn to formulate strategies to prevent, as opposed to developing fears and avoiding walking behaviors that might trigger them. The pelvic mechanism also allows movement of the COM in all 3 planes through 6 degrees of freedom (DOF). Unlocking the DOFs enables the individual to explore their limits of stability, whereas locking the DOF provides external stability for those with poor balance. This feature is unique in comparison with other robotic devices, which offer limited mobility or mobility in only one plane [36]. A trunk harness also secures the individual's trunk when they walk inside the device and prevents excessive forward lean. The KA requires a short participant setup time (5-10 min) with assistance of only 2 individuals, due to a simple computerized user interface and an easily customizable pelvic mechanism. In comparison, more sophisticated robotic treadmill gait trainer systems or nontreadmill-based robotic exoskeleton systems tend to have a long setup time and require more than 2 individuals to help set up a participant [37-39]. We have previously published details on walking biomechanics in the KA interface and its different modes in another paper [24]. However, for this study, we used

3 distinct modes of the KA treadmill interface with and without varying levels of BWS:

1. Intent-driven mode: Uses the KA's force-velocity software relationship, which allows participants to drive the belt at their self-selected CWS.
2. Joystick mode: Enables the researcher/therapist to control (externally) the speed of the treadmill belt using a joystick controller. This mode is similar to a typical motor-driven treadmill; however, the operator is able to impose smooth or abrupt speed transitions via the KA software. We used this mode during HF+C training for speeding up and slowing down tasks.
3. KA software modifications: In either of the aforementioned modes, we used the KA software to create some of the 9 essential challenging mobility for the HF+C group. For example, using the joystick mode, we could additionally program variable speed changes, which abruptly changed the speed of the motorized treadmill belt at random intervals. In another instance, we programmed perturbations that disrupted an individual's forward progression, while walking in the intent-driven mode.

Training Paradigms

Hands-Free Body Weight Support Gait Training

This group served as our "control," in that participants did not perform any additional essential challenging mobility skills during their 6-week training period. We felt that the inclusion of an active training control group was necessary to determine if adding essential challenging mobility skills practice to a gait training program would improve walking outcomes above and beyond improvements gained from walking practice alone.

However, it is important to note that because of the safety features of our robotic device, we were able to eliminate provision of handrail support and/or manual assistance from the clinician. Although walking upright with handrail support can provide sufficient training challenge and fall safety, because of poor hemiparetic trunk control stroke, survivors are likely to adopt stooped postures by leaning forward and holding onto handrails for trunk support [40]. Such postures not only decrease training intensity and metabolic output but also minimize functional improvements [41,42]. Thus, treadmill training without handrail support can offer a more practical dynamic balance challenge that pertains to real-world independent ambulation. In addition, we did not offer participants any walking instructions (eg, how to step or correct their movements) and did not offer any passive assistance during training. Our governing principle regarding walking rehabilitation post stroke was to provide the individual with a safe environment to practice walking, solve the problem, and learn from mistakes during training. We followed AHA guidelines for exercise training [16]. Participants in this group walked for a total duration of 30 min per session, at 60% to 80% of their heart rate (HR) reserve (ie, moderate to high intensity) based on the Karvonen formula [43] with or without their prescribed BWS level (ie, between 0 and 30% support; assigned as described below). By taking advantage of the KA interface's safety mechanism and DOF, participants in this group were able to explore their limits of stability while controlling the treadmill belt speed, and thus, train independently without assistance or external support.

Challenge With Hands-Free Body Weight Support Gait Training

This group served as our "experimental" group, in that participants additionally performed 9 different essential challenging (C) mobility skills, along with HF walking during their 6-week training period (Table 1). The purpose of practicing these 9 essential training challenges along with HF walking was to offer participants opportunities to navigate through common environmental hazards that they may encounter during community ambulation. This protocol was innovative, as it involved exposing stroke survivors to challenging tasks that required strong skills in anticipatory and reactive balance and functional mobility. The KA's safety features allowed us to provide participants with this experience and to treat losses of balance or stumbles as "learning experiences," from which participants could learn to formulate new strategies without any negative consequences. At the start of each training week, the program coordinator would randomly select and assign 3 challenges for each session using a random number generator [27]. Participants practiced training for each of the 3 skills for 30 min (10 min per skill), without handrail support at 60% to 80% of their HR reserve intensity per session. We did not have a prescribed challenge progression for each skill; however, we encouraged participants to perform each skill at a level that was challenging for them (see task difficulty, Table 1).

Intervention Protocol for Each Training Session

This training protocol comprised 6 weeks of 18 total training sessions for both groups (summary in Table 2). Each group trained 3 times per week with alternate rest days to prevent undue fatigue.

Participant Body Weight Support Level Determination for Each Training Session

We used a unique approach to determine BWS levels for all participants for each training session. Instead of automatically applying a specific level of BWS for all participants, we instead allowed BWS to vary per training day, depending on the participant's fastest CWS inside the device. At the start of each session, participants walked in the self-drive mode for 5 m at 4 different levels of BWS (0%, 10%, 20%, and 30%). Some of the taller individuals were unable to use 30% because of height constraints of the KA (n=5). We calculated 10-m walk speed at each level of BWS and selected the participant's fastest CWS using a speed difference of ≥0.08 m/s faster than 0%. The participant used this level of BWS to train for the session. This method ensured each participant's BWS levels were individualized, unbiased, and varied according to their optimal walking speed performance. We were interested in whether participants would gradually decrease BWS over the duration of the training protocol.

Participant Training Intensity Heart Rate Zone Determination for Each Training Session

We documented all participant's baseline blood pressure and HR before commencement of each training session. We calculated the maximum HR for each participant using their age (ie, $HR_{max}=220 - age$) and calculated the desired 60% to 80% training intensity using the Karvonen formula (ie, training intensity=(max HR − resting HR) × (desired %) + resting HR) based on AHA training recommendations [16]. If the participant was taking a beta-blocker, we revised this formula to use a max HR calculated as $HR_{max}=164 - age$ [44]. Thus, we individually customized the participant's training intensity for each session. We encouraged participants to walk fast enough during training to achieve these zones; however, we also measured rating of perceived exertion (RPE; see below) to obtain a proxy measure of training intensity in the event that HRs did not reach the desired intensity. We used a GARMIN HR monitor that was strapped to each participant's chest to record actual HR measurements for each session. We recorded HR values each minute; thus, we recorded a total of 30 HR values per training session (6×5-min bouts=30 min).

Recording Training Intensity Rating of Perceived Exertion for Each Training Session

We used the Borg Scale (ie, 6 to 20) [45,46] to solicit RPE values from participants every 2 min during training. We were interested not only in participants' general perceived training difficulty but also in which of the 9 skills would elicit the highest RPE values from participants in the HF+C group.

Table 1. Description of the 9 essential locomotor challenges used in training the challenge and hands-free (challenge with hands-free walking) group.

Challenge task	KineAssist interface mode	Rationale	Training practice	Task difficulty
Long stepping	KA[a] self-drive mode	To step over common environmental hazards, for example, puddles	Using infrared laser beams, we defined a visual line on the treadmill surface in front of the participant's feet participants instructed to take long steps, such that the heels of both feet crossed the line	If the participant was able to consistently step over the line, the distance was increased by 1-inch increments
Speeding up and slowing down	KA joystick mode	To improve the ability to speed and slow down during ambulation	The training staff the controlled the belt speed for 20 s at individual's CWS[b], 20 s at double their CWS, and 20 s at CWS per each minute of training	If the participant was able to successfully keep up with the fast speed, the top speed increased by 0.2 m/s
Head turns	KA self-drive mode	To simulate the need to look in different directions while walking in the community	Participants walked at their CWS. Every 10 s, staff provided instructions to turn the head either right, left, up, or down, and maintain it for 10 s	If the participant maintained walking speed with head turns, they were instructed to shake their head side-to-side or up/down for 10 s each
Variable walking speeds	KA joystick mode	To improve reactionary balance and gait speed control	KA software controlled the treadmill belt speed within a range of the participants' CWS±0.2 m/s. Participants adapted to abrupt changes in speed	If the participant was able to successfully maintain balance and walk comfortably, speed ranges were increased by 0.2 m/s
Hurdles	KA self-drive mode	To improve ability to step over objects in the environment (eg, curb)	Participants were instructed to walk at their CWS while stepping over a hurdle positioned at height to challenge foot clearance; 5 min practice per foot	If participants consistently cleared the current hurdle height, height increased by 1-inch increments
Perturations	KA self-drive mode	To improve reactionary balance control	Participants were instructed to walk at their CWS, while experiencing abrupt disturbances (ie, brief backward accelerations) to forward progression delivered by the KA software	If participants walked through forward perturbations without experiencing disturbances (ie, missteps or backward steps), the intensity of the perturbation would be increased
Backward walking	KA self-drive mode	To improve balance control, simulate instances where stepping backward to maneuver over obstacles	Participants walked backward	If the participant successfully walked backward, they were encouraged to step faster
Walking with foam shoes	KA self-drive mode	To improve ability proprioception, to walk on uneven surfaces, and stepping height	Participants walked with foam shoes strapped to their typical footwear. Shoes ranged from 2 to 6 inches in thickness	If the participant successfully maintained their CWS, the height of the foam shoes increased from 4 to 6 inches in thickness
Narrow stepping	KA self-drive mode	To decrease reliance on external support and improve dynamic balance	Participants walked on a straight infrared while taking narrow steps at their self-selected CWS without hand support or manual assistance	If the participant successfully maintained their CWS, they were verbally encouraged to walk faster

[a]KA: KineAssist.

[b]CWS: comfortable walking speed (m/s).

Table 2. Summary of the hands-free and challenge with hands-free walking intervention training parameters.

Intervention	Hands-free walking	Challenge+hands-free walking
Duration	6 weeks	6 weeks
Total sessions	18 sessions	18 sessions
Weekly training	3 days a week	3 days a week
Session duration	1 hour	1 hour
Intervention duration	30 min	30 min
Training speed	Comfortable walk speed at chosen BWS[a] level	Comfortable walk speed at chosen BWS level
Intervention goal	Perform 30 min of walking at fastest 10MWT[b] with/without BWS as prescribed	Perform 30 min of walking at fastest 10MWT with/without BWS while performing additional walking skills
Session design	5-min bouts × sets, or as long as continuously tolerated	5-min bouts × 6 sets, or 10-min bouts × 3 sets to allow for skill changes
Session goal	Target 60% to 80% of heart rate reserve during all trials	Target 60% to 80% of heart rate reserve during all trials
Locomotor challenge	Hands-free and without manual assistance	3 new randomized locomotor total challenges per day × 3 sessions=9 per week
Instruction	Maintain heart rate in the target zone while walking	Maintain heart rate in the target zone while performing different walking skills
Physiological measures monitored	Heart rate—using heart rate, monitor each minute; rate of perceived exertion—using Borg scale every 2 min; blood pressure—pre/post	Heart rate—using heart rate monitor each minute; rate of perceived exertion—using Borg scale every 2 min; blood pressure—pre/post
Additional session measurements	Total number of steps (using step watch) and distance covered (using distance wheel)	Total number of steps (using step watch) and distance covered (using distance wheel)
Rest breaks	Every 5 min if necessary; standing breaks if heart rate exceeded zone; voluntary breaks if requested by participant (rare)	Every 5 min if necessary; standing breaks if heart rate exceeded zone; voluntary breaks if requested by participant (rare)
Training personnel	Physical therapist × 1; research assistant × 1	Physical therapist × 1; research assistant × 1
Training setting	Clinical laboratory	Clinical laboratory

[a]BWS: body weight support.

[b]10MWT: 10-meter walk test.

Recording Total Number of Steps Taken and Distance Covered per Training Session

For both groups, we recorded the total number of steps taken per session using a step watch (Orthocare Innovations), strapped around the participant's nonaffected ankle. We also recorded the total distance covered per training session using a Stanley distance wheel. We positioned and secured the wheel at the front of the treadmill belt and measured the distance of the moving belt while the participant walked during their training session.

Session Duration, Approach, and Progressions

Although participants in both groups had to complete 30 min of training, each single session lasted for a total of 90 min. This included the time for baseline and post measurements/calculations (ie, blood pressure and HR), setting up the HR monitor, determination of BWS level for training, and intervention trials with/without rest breaks. Although we encouraged participants to continuously train for 30 min, we recognized that participants might not have the necessary cardiovascular endurance to continually train for 30 min. Hence, we divided each training session into six 5-min bouts. We gave

participants the option to take a seated or standing rest break after completion of each 5-min bout or combine multiple bouts (ie, 10 or more continuous minutes) followed by a rest. Thus, participants could individualize their training sessions, according to their comfort and ability. We encouraged all participants, regardless of their starting point, to aggregate more bouts as they progressed with training. Research assistants, conducting the training session, verbally encouraged participants while training to maintain their CWS and finish each training bout. However, they did not provide any manual assistance or external support during training.

Criteria for Successful Training Session Completion

Although we encouraged all participants to complete their target 30 min of training per session, we used a threshold mark of 20 min to deem a session as "complete" and include it as a data point. If a participant did not achieve the minimum of 20 min, they had to repeat the session. At the completion of each session, we documented the above-described variables and entered them into a database. The PI and program coordinator monitored this database to ensure adequate study progress and safety of all participants.

Total Time Taken for Each Training Session Visit

Participants on an average spent 1 to 1.5 hours per training session. This included the time for evaluation and measurement of baseline parameters (blood pressure and HR), choosing appropriate BWS level, training for 30 min (including rest breaks), and final posttraining blood pressure, HR measurement, restroom breaks, and drop-off and pick-up wait. We, thus, instructed participants to keep aside 2 hours on the days they were training and up to 3 hours on the days they were assessed.

Participant Compensation

Participants were compensated US $10 per hour for the days that they trained and were assessed.

Participant Adherence and Missed Session Makeover

Our goal was to provide adequate rest by alternating training days with rest days per week. To support participant adherence, the program coordinator worked with participants to pick alternate training days (3 times a week) and time slots during those days that suited the participant's schedule. However, if a participant was not able to attend their session, we rescheduled it for 1 of the 2 free days of their training week. We requested participants to keep at least 2 hours aside for training on the days that they committed to come, and up to 3 hours aside for the days they would be assessed. We instructed participants that it was critical that they did not miss any training sessions and enrolled participants only after they had finished any travel obligations that would have interfered with their training. In addition, the program coordinator would also call and remind participants, a day before their training session, to come for training. If participants did not have a personal means of transport to come to the LocoLab for training, we arranged for alternate local public transport options, for example, local government run bus/van service. We also limited participants from rescheduling and extend their training sessions to a maximum of 7 consecutive weeks, to complete their 18 sessions, taking into account any rescheduled sessions because of personal commitments and/or national holidays. Participants were allowed a total of 5 rescheduled sessions.

Minimizing Variability in Application of Procedures

We ensured that a minimum of 2 research staff members, one being a physical therapist, trained every participant during each training session. In total, we had 10 different research staff members, including 3 physical therapists, who regularly rotated and conducted all the training sessions to minimize expectation bias. The PI oversaw all training sessions and ensured strict adherence to all training protocols for both groups. The program coordinator and PI reviewed the progress of both training groups weekly and checked if all data were correctly documented. We ensured that no cointervention contamination occurred, by asking participants to refrain from attending any active lower limb physical therapy programs or participating in any walking intervention studies outside of our study.

Reporting of Adverse Events

We defined an adverse event as an event that occurred during or after the training session when the participant was at the training site and trained staff members to report any adverse event pertaining to:

1. Fall to the ground (defined as an unintentional loss of balance)
2. Any symptoms of angina or myocardial infarction
3. Any musculoskeletal injury during/after session training
4. New stroke or transient ischemic attack
5. Hospitalization for any cause
6. Death due to any cause.

Participants were also encouraged to report any symptoms (pain, soreness, numbness, etc) or signs of injury (inflammation, blisters, etc) that they experienced following training on returning home.

Standard Precautions

We used the same standard precautions for both training groups and modified them for each individual participant, after evaluation and recommendation by the PI. These included the following:

1. Decrease in exercise intensity for systolic blood pressure greater than 200 mm Hg or diastolic blood pressure greater than 100 mm Hg.
2. Decrease in exercise intensity, if HR was greater than 75%.
3. Pause in training on observation of dyspnea or if blood pressure dropped below resting pressure.
4. Pause in training if participant reported symptoms of light-headedness.

Assessments

We used various functional mobility assessments at different time points - pretraining (baseline), midterm, posttraining (final), and 6-month follow-up, conducted by the physical therapist on our study at the LocoLAB. We used the 10-meter walk test to measure participants' CWS and fast walking speed (FWS) [47], and the 6-min walk test (6MWT) [48] to measure walking capacity using an 85-feet oval walkway. At baseline, participant's hemiparetic severity and ambulation category were classified using the lower extremity Fugl-Meyer, and functional ambulation category scale [49], respectively. We also used the Mini-Mental Scare Examination as a screening tool for participants' cognitive function (>24) [50]. We also used the Berg-Balance Scale (BBS) [51] and Dynamic Gait Index [52] to measure participants' balance function. We used the Activities-specific Balance Confidence (ABC) scale [53] to evaluate participants perceived balance function during activities of daily living, and the Geriatric Depression Scale (GDS) [54] and Stroke Impact Scale (SIS) [55] to assess participant's mental function and perceived impact of poststroke disability on their quality of life, respectively. Participants were assessed at baseline, midterm, final (after 6 weeks), and at 6-month follow-up. Table 3 describes the assessments performed during these periods.

Table 3. Timeline for assessments and collection of outcome variables at various study stages.

Baseline	Midterm	Final	6-month follow-up
Comfortable walk speed (CWS)	CWS	CWS	CWS
Fast walk speed (FWS) using	FWS	FWS	FWS
10-meter walk test (10MWT)	6MWT	6MWT	6MWT
6-min walk test (6MWT)	BBS	BBS	BBS
Fugl-Meyer lower extremity score	GDS	GDS	GDS
Functional Ambulation Category	—	DGI	DGI
Berg Balance Scale (BBS)	—	ABC	ABC
Dynamic Gait Index (DGI)	—	SIS	SIS
Geriatric Depression Scale (GDS)	—	—	—
Stroke Impact Scale (SIS)	—	—	—
Activities-Specific Balance Confidence (ABC)	—	—	—
Mini-Mental State Examination (MMS)	—	—	—

Primary Outcome Measure

As change in over-ground CWS is an important, valid, sensitive, and reliable measure of poststroke recovery and walking function [56], we chose difference in CWS between groups, from pre- to posttraining as our primary outcome measure [57,58]. On the basis of our power analysis, we planned to include baseline-walking speed as a covariate, if it was significantly related to CWS at pre- and posttraining.

Secondary Outcome Measure

We plan to report descriptive data on the following secondary exploratory outcome measures: FWS, 6MWT, BBS, GDS, SIS, and ABC scores, with mean and SDs. However, we will not include these variables in our main analysis, as we are not appropriately powered to include them.

Subgroup Analysis

In addition to these main assessment measures, we also recorded BWS levels, HR, and RPE exertion changes, total number of steps, and distance covered during each session, for participants in both training groups. Descriptive data analysis along with subgroups comparative analysis will be performed on these variables, from pre- to postintervention and on a week-by-week basis, and will be reported in another manuscript. We will also assess feasibility and compliance of each group to either intervention, along with ability to maintain target HR intensity during training. These subgroup analyses will help in better understanding the impact of training on functional walking outcomes and impact on community ambulatory function.

Survey Data Analysis

Participants in both groups also completed our custom-designed study survey at the end of each training week. The survey consisted of questions on the 9 essential challenging mobility skills that we identified using the research criteria specified by Patla et al [25]. The survey questionnaire consisted of the following 3 subparts: (1) identify which of the 9 essential challenging mobility skills you have difficulty with in your daily life (using yes/no responses); (2) rank in order of

importance (1-9), which of the 9 essential mobility skills is most important for you in improving walking function; and (3) respond to specific questions on your training experiences (using a Likert scale 1-7; see Multimedia Appendix 2). We will assess survey data responses for change in responses, ranking of task difficulty, and change in Likert scale scores, respectively.

Criteria for Data Analysis

We will only be considering those participants in our final analysis, as a data point, if they completed their first week of training. Participants will not be included in our final analysis if they were unable to complete the first week of training, for reasons such as personal time limitations, conflicting time commitments, family crises, and personal psychological factors such as depression and medical procedures.

Results

Total Participants Enrolled in Our Study

We assessed 77 individuals with chronic mild to moderate hemiparesis, and excluded 38 individuals who did not meet our inclusion criteria, from June 2012 to January 2015. We enrolled and randomized a total of 39 individuals post stroke for our study, with 19 participants in the HF group and 20 participants in the HF+C group. Data collection along with 6-month follow-up continued until January 2016. Detailed results of this study will be presented in 2 subsequent manuscripts.

Proposed Statistical Methods

We will assess normality and homogeneity of data for all outcome measures in both groups. If possible, we plan to conduct an intention-to-treat analysis. We will compare our primary measure in both groups from pre- to postassessment using an ANCOVA at a significance level of $P<.05$, with the covariate being baseline CWS, if significantly related to change in CWS from pre- to posttraining. As all our secondary outcome measures are exploratory in nature, we will use a repeated measures design for comparing changes from baseline, midterm, final assessment, and at 6-month follow-up, at a significance level of $P<.05$, with post hoc analysis. For our survey data, we

will compare changes between the first and last training sessions using Spearman correlation for the yes/no responses question, a Wilcoxon rank-sum test for the rank order question, and chi-square analysis for Likert scale responses. A subsequent manuscript will have detailed description of our data analysis methods and statistical tests.

Discussion

Locomotor disability post stroke continues to impede stroke survivors from engaging in active community participation and negatively impacts their quality of life. Given the prioritization of improvement in walking function by stroke survivors and the 2014 AHA exercise training recommendation report, it is all the more vital that poststroke gait interventions incorporate task-specific essential challenging mobility skills, akin to real-world scenarios, along with training at higher cardiovascular intensities to improve functional gains [59]. Through our study, we explored 2 unique gait interventions, ie, HF walking and HF+C walking, using a novel and safe gait training environment to investigate functional ambulation capacity after 6 weeks of training. Our study results will yield important insight on whether individuals post stroke can train at higher intensities, especially while walking without any external handrail support or passive manual assistance at their preferred self-selected BWS level (HF walking) or when practicing essential challenging mobility skills with HF walking (HF+C walking). Although our primary outcome measure is change over-ground CWS, we have also collected various secondary exploratory measures and survey data for both training paradigms. As our secondary measures are most commonly used in clinical settings to assess functional ambulatory capacity, we hope these variables will inform future poststroke studies that plan to use similar gait training paradigms. Our main study outcomes and week-by-week training analysis are being presented in 2 separate manuscripts, respectively. We hope that the results of this study will help in better informing clinicians and researchers on how real-world balance challenges can be incorporated to improve the selection of treadmill training protocols to improve functional walking capacity for individuals post stroke.

Authors' Contributions

DAB and EJR conceived the study; DAB acted as the PI, and EJR was a coinvestigator. AN assisted in training protocols and data collection and drafted the manuscript. All authors contributed to editing the manuscript, read, and approved the final manuscript.

Conflicts of Interest

DAB is a consultant to HDT Global, the company that markets and sells the device mentioned in this paper. DAB is also a named inventor on the intellectual property associated with the device and does receive royalties for any sales of the device. AN and EJR do not have any conflicts of interests to declare.

Multimedia Appendix 1

Participant Phone Screen Form.

[PDF File (Adobe PDF File), 32KB - resprot_v7i5e118_app1.pdf]

Multimedia Appendix 2

Weekly Community Walking Survey.

[PDF File (Adobe PDF File), 56KB - resprot_v7i5e118_app2.pdf]

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Abbreviations

6MT: 6-min walk test

10MWT: 10-meter walk test

ABC: Activities-Specific Balance Confidence scale

AHA: American Heart Association

ANCOVA: analysis of covariance

BBS: Berg Balance Scale

BWS: Body weight support

COM: center of mass

CWS: comfortable walking speed

DOF: degrees of freedom

FWS: fast walking speed

GDS: Geriatric Depression Scale

HF: hands-free

HF+C: challenge and HF walking

HR: heart rate

KA: KineAssist

KA interface: KineAssist treadmill interface

PI: principal investigator

RPE: rate of perceived exertion

SIS: Stroke Impact Scale

UAB: University of Alabama at Birmingham

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Protocol

Effect of Rebound Exercises and Circuit Training on Complications Associated with Type 2 Diabetes: Protocol for a Randomized Controlled Trial

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Abstract

Background: The incidence of type 2 diabetes mellitus, a chronic lifestyle disease, and its complications are on the rise. Exercise has been documented as being effective in the management of musculoskeletal pain, depression, and reduction of hyperglycemia in diabetic patients. However, there is no consensus regarding the types of exercise that reduce musculoskeletal pain and depression and improve quality of life as well as respiratory function among individuals with type 2 diabetes.

Objective: The objective of this study is to determine the effects of rebound and circuit training on musculoskeletal pain, blood glucose level, cholesterol level, quality of life, depression, and respiratory parameters in patients with type 2 diabetes mellitus.

Methods: A total of 70 participants are expected to be recruited in this single blind randomized controlled trial. Computer-generated random numbers will be used to randomize the participants into 3 groups, namely, the rebound exercise group, the circuit exercise group, and the control group. Measurements will be taken at baseline and at the end of the 8 weeks of the study. Participants' musculoskeletal pain will be assessed using the visual analog scale, quality of life will be assessed using the SF 12 Health Survey Questionnaire, depression using the Beck Depression Inventory, respiratory parameters using the spirometer, and biochemical parameters such as glucose level and cholesterol level using the glucometer. Data will be analyzed using descriptive statistics and inferential statistics of multivariate analysis of variance between the groups and paired t test within the group. Alpha will be set at .05.

Results: The results of this study will identify the effectiveness of rebound exercise and circuit training, compared with the control, in the management of type 2 diabetes mellitus and on quality of life, musculoskeletal pain, depression, glycemic control, cholesterol level, as well as improvement in respiratory function.

Conclusions: Though different additional strategies such as exercise and dietary and lifestyle modifications exist for the control of type 2 diabetes, they are mostly applied for the control of glucose level. No strategies have been identified for the control of complications associated with diabetes such as musculoskeletal pain, depression, and reduction in quality of life.

Trial Registration: Clinicaltrials.gov NCT03200795; https://clinicaltrials.gov/ct2/show/NCT03200795 (Archived by WebCite at http://www.webcitation.org/6mBgcj6z7)

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Introduction

Overview

Diabetes is a global epidemic disease [1]. The global prevalence of diabetics is currently estimated to be 415 million and is projected to rise to over 642 million by the year 2040, with Asians suffering the bulk of the total diabetes epidemic [2]. The International Diabetes Federation (IDF) estimated that there were 14.2 million diabetes patients living in Africa in 2015, excluding the 67% of patients that are undiagnosed, and the projection rate is expected to rise to 34.2 million by 2040 [2]. South Africa is among the most populous African countries with the highest number of people with diabetes with 2.3 million people, followed by Democratic Republic of Congo 1.8 million, Nigeria 1.6 million, and Ethiopia 1.3 million. Nearly half of the adults with diabetes live in these countries. In South Africa, the prevalence of diabetes mellitus (DM) is estimated to be about 6%, excluding the undiagnosed cases, whereas 9% of the population has prediabetes. DM accounts for 58 deaths daily and is the fifth highest cause of natural deaths [3]. The highest prevalence of diabetes is among the Indian population (11%-13%), as this group has a strong genetic predisposition to diabetes. This is followed by 8% to 10% in the colored community, 5% to 8% among blacks, and 4% among whites. The prevalence of diabetes in the public health sector of KwaZulu-Natal was found to be 14.3% higher than the national prevalence estimates [3].

Diabetes is a systemic disease that affects multiple body functions and structure. The typical spectrum of problems of patients with DM can now be defined based on the International Classification of Functioning, Disability and Health (ICF). For practical purposes and in line with the concept of condition-specific health status measures, DM problems can be classified as follows: body function as hematological system function, sensation of pain, musculoskeletal system, and respiratory system. On the basis of activities and participation restriction, DM problems can be classified as quality of life (QoL) and psychosocial factors. These will serve as a guide in clinical studies with DM or as a guide to multidisciplinary assessments in patients with DM [4].

In 2004, the US National Health Interview Survey reported that 58% of diabetic patients would have a functional disability [5]. The percentage of diabetic patients with a functional disability will increase as the number of diabetic patients increases and will constitute a major public health problem. Recent data show that the prevalence of musculoskeletal pain (MSKP) manifestations in the hands and shoulders in patients with type 1 or type 2 diabetes is 30%. These manifestations are closely linked to age [6] and prolonged disease duration [7,8].

Musculoskeletal disorders are very common in diabetes and are associated with poor glycemic control and more complications. Assessment of musculoskeletal disorders among diabetics should include an estimate of cholesterol, glycemic control, MSKP, respiratory parameters, and QoL.

People with diabetes are at twice as high a risk of suffering from premorbid depression as the general population [5]. The coexistence of depression in people with diabetes catalyzes serious disease comorbidities, MSKP, decreased respiratory capacity, poor glycemic control which may lead to hyperlipidemia and poor QoL, and escalated health care expenditures [9]. Depressive symptoms are more likely to persist among persons with multiple diabetic-related complications such as musculoskeletal disorders. Increase in pain may lead to increased depression and reduction in respiratory capacity and QoL. Studies have shown that both exercises and pharmacotherapy [10] can decrease depression and improve glycemic control and overall QoL in persons with diabetes and thus, in addition, provide substantial financial savings and improved medical care for these individuals.

Exercise, in addition to diet modification and medication, has long been recommended as one of the 3 main components of diabetic therapy [11]. The low cost and nonpharmacological nature of exercise enhances its therapeutic appeal among type 2 diabetic patients. Published exercise intervention trials [12-15], using different types of intervention, usually have small sample sizes and the findings of their studies have varied. The optimal type, frequency, intensity, and duration of exercise for achieving therapeutic goals in type 2 diabetes are not known. The psychosocial variables and cardiorespiratory-related health of diabetics appear to be underexplored in exercise-related interventions [11]. Moreover, prospective randomized controlled trials (RCTs) on the effects of exercise in the prevention or treatment of musculoskeletal complications and disability seen in diabetes patients are needed [16].

Exercise has been documented as effective in the management of MSKP; however, there is no consensus regarding the type of exercises that improve MSKP. The effectiveness of exercise in reducing MSKP as well as depression and in improving respiratory function among individuals with type 2 diabetes has not been documented.

Rebound exercise is a type of exercise that can aid the management of type 2 diabetes [17] and is likely to improve MSKP and depression. Circuit resistance training (CRT) has recently been documented to be safe in the management of type 2 diabetes; however, its effects on MSKP and depression have not been assessed [1]. Rebound exercise on the mini trampoline moves all parts of the body at once, so it is also called cellular exercise [18]. It may be superior to any other type of exercise as it utilizes gravity and forces of acceleration and deceleration so that at the top of the bounce one experiences weightlessness and at the bottom the weight doubles pulling into the center of the rebounder. Rebound exercise is also a form of aerobic exercise that increases oxygen consumption and stimulates immune response.

Circuit training is a combination of strength training and aerobic exercises. Strengthening exercise is a resistance exercise that helps to keep the muscles flexible and strong and also strengthens the bones. Aerobic exercise, on the other hand, is

a less vigorous exercise that increases oxygen consumption; the increase in oxygen consumption helps to burn more calories and stimulates immune response and cardiovascular health [19]. Rehabilitation can assist to retain physical and functional abilities as well as control psychological emotions [20]. Therefore, comprehensive rehabilitation to manage diabetes-related complications that encompasses exercises such as rebound and circuit training may improve glycemic control, reduce depression, and improve QoL and musculoskeletal functions.

Theoretical Framework

Previous studies have assessed the effect of combined resistance and aerobic exercises on type 2 DM patients and observed significant reductions in HbA_{1c} [21-23]. However, Geirsdottir et al [24] did not observe any favorable changes in fasting glucose or HbA_{1c} in patients with type 2 diabetes. Therefore, there is no consensus on the effect of CRT in type 2 diabetes. Rebound exercise has been documented to be effective in reducing plasma fasting glucose, HbA_{1c}, and body mass index (BMI) in type 2 diabetes. It is also simple, inexpensive and enjoyable [23]. Moreover, it has been documented to improve QoL in patients with type 2 diabetes [17]. However, its effect on MSKP, respiratory parameters, and depression has not been documented. Prospective RCTs on the effects of exercise in the prevention or treatment of musculoskeletal complications, cardiorespiratory parameters, and psychosocial variables seen in diabetes patients are needed [16]. In African countries, there is a paucity of reports that describe musculoskeletal disorders in diabetic patients. To the best of our knowledge, no clinical trial has been conducted that compares the effect of rebound exercises and circuit training on MSKP, respiratory parameters, and psychosocial variables among patients with type 2 diabetes. No previous studies had been conducted to assess the effect of any treatment or prevalence of MSKP manifestations in diabetic patients or to evaluate the predisposing factors. This study is, therefore, proposed to determine the effect of rebound exercises and circuit training on MSKP, as well as selected biochemical and psychosocial factors among individuals with type 2 diabetes.

Objective

The objective of this research is to investigate the effect of rebound exercises and circuit training and compare them to the routine care of type 2 diabetic patients. The objectives of this research are as follows;

1. To investigate the effect of rebound exercises on glycemic control, cholesterol level, respiratory parameters, pain scores, depression, and QoL among type 2 diabetes patients
2. To investigate the effect of CRT on glycemic control, cholesterol level, respiratory parameters, pain scores, depression, and QoL among type 2 diabetes patients
3. To investigate the effect of routine care (control group) on glycemic control, cholesterol level, respiratory parameters, pain scores, depression, and QoL among type 2 diabetes patients
4. To compare the effect of circuit training, rebound exercises, and routine care on glycemic control, cholesterol level,

respiratory parameters, pain scores, depression, and QoL among type 2 diabetes patients.

Methods

Study Design

The study is a single-blind, parallel RCT. RCTs are quantitative, comparative, controlled experiments in which investigators study 2 or more interventions in a series of individuals who receive them in random order. The RCT is one of the simplest and most powerful tools in clinical research.

Participants

The participants for the study will be patients diagnosed with type 2 diabetes by the attending physician at King Edward Hospital. Participants will be considered eligible if they have been diagnosed with type 2 diabetes for at least 4 years and have been on oral hypoglycemic control. They will be recruited consecutively as they are available through the outpatient endocrinology clinic of the hospital by a member of the research team. Only participants with MSKP and depression will be included in the study. They will be screened for MSKP using the Nordic Musculoskeletal Symptoms Questionnaire and for depression using the Beck Depression Inventory (BDI). The participants must be aged between 20 and 55 years. Those within this age limit are considered to be adults with musculoskeletal affectation, as indicated by Nordic Musculoskeletal Symptom Questionnaire, and with at least ≥11 score on the BDI. Only participants who meet the inclusion criteria will be considered for the randomization into the groups. The consent of the participants will be sought before they participate in the study.

Patients will be excluded from the study if they are involved in sporting activities or if their musculoskeletal problems are severe and may prevent them from performing some of the exercises. Moreover, individuals with hypertension, coronary artery disease, or myocardial infarction; or who have had cardiac or abdominal surgery within the previous 6 months; or who have a history of fractures of the spine, hip, knee, or ankle joints; as well as those with lower limb weakness and deformities with a loss of protective sensation in the feet will be excluded. Similarly, pregnancy or lactation, use of insulin, and the presence of retinopathy or nephropathy will make a patient ineligible. Finally, subjects who do not consent to participate will be excluded from the study. Participants who meet the inclusion criteria will be randomized into 1 of the 3 groups of the study.

Setting

The research will be conducted at the Performance Laboratory of the Department of Physiotherapy, School of Health Sciences, University of KwaZulu-Natal. The participants will be recruited from the King Edward Hospital, Durban. King Edward Hospital is a tertiary hospital that provides specialist services to the people of KwaZulu-Natal. It is located in Durban City, Ethekwini Municipality, KwaZulu-Natal Province, South Africa.

Study Team

The study team will consist of 4 physiotherapists, of which 2 are clinicians and the other 2 are both clinicians and researchers.

The team will also include an endocrinologist who is a physician with 10 years of research experience. In addition, 2 among the physiotherapists will be research assistants and they will administer the treatment. The endocrinologist will screen the patients and ensure that they take the same medications and that they are medically fit, whereas the researchers will screen the participants to ensure that they meet the inclusion criteria.

Intervention

The study will comprise 3 groups; the rebound exercise group, the circuit resistance exercise training group, and the routine care group (the control). The routine care group will undergo one exercise training after 8 weeks of enrollment. Participants will be monitored for subjective fatigue, dyspnea, respiratory distress, profuse sweating, or unsteady gait during the exercise activities, as these may be indications that they have reached maximum exertion.

Rebound Exercise Group

Participants randomized to this group will be instructed on the proper techniques of the desired movements (hopping) on the rebounder. All instruction and training will be provided by the research assistants who are physiotherapists practicing in South Africa. They will teach the participants how to rebound during the session. To ensure exercise endurance, patients allocated to this group will complete a 6-min walk test (6MWT), as prescribed by the American Thoracic Society [25], which will be conducted along a straight 40-m Department of Physiotherapy passageway. On successful completion of the 6MWT, patients will be given an opportunity to familiarize themselves with the equipment. Each participant will undergo 3 sessions a week for 8 weeks, with each session lasting between 15 and 25 min.

The exercise will involve bouncing on the center portion of a mini trampoline (2013 Portable Model Half-Fold Cellerciser) with feet slightly apart and knees in full extension. Each foot strike equals one step or bounce with step height. This will be defined as the distance between the foot at a maximum height of the jump and the bed of the center of the trampoline ranging between 10 and 15 cm [23]. Exercise durations were set at 5-min intervals with 3-min rest periods. Each exercise program session will last 15 min with 9 min of rest for the first 4 weeks, progressing to 25 min with 15 min of rest in the subsequent 4 weeks, 3 times per week over 8 weeks.

Bouncing frequency will be determined by signals from a metronome and will be set at between 90 and 120 bounces per minute. Heart rate training zone will be maintained during the exercise at a moderate intensity of 40% to 60% and will be calculated using the Karvonen formula ([heart rate reserve×training percentage]+resting heart rate) [23]. The heart rate will be monitored using the heart rate monitor (Polar Electro Oy) that will display the participant's heart rate and emit a warning signal if the heart rate goes outside the prescribed training zone, thus serving as a guide and indicator for the participant to adjust the steps and bounce while on the trampoline. In addition, the Borg scale will be used to assess the rate of perceived exertion.

Circuit Exercise Group

The circuit exercise for the participants in this group will be designed for each participant. To ensure exercise endurance, patients allocated to this group will complete a 6MWT, as prescribed by the American Thoracic Society [25], which will be conducted along a straight 40-m Department of Physiotherapy passageway. On successful completion of the 6MWT, patients will be given an opportunity to familiarize themselves with the circuit exercise equipment. Exercise sessions will take place 3 times a week for 8 weeks. The participants will undergo 10 min of warm up before and 10 min of cool down after the training. The stations for circuit training include 2 stations—1 and 2. Station 1 is the resistance exercise, whereas station 2 is the aerobic exercise with the bicycle ergometer. Station 1 comprises the following 6 substations: station A—bench press, station B—seated row, station C—lateral pull down, station D—biceps forward, station E—front thigh and back thigh, and station F—leg press. Resistance exercises will be performed on weight machines. Throughout the resistance training program, participants will rotate among the different machines until they have used every one: the bench press, seated row, lateral pull down, biceps forward, front thigh, back thigh, leg press, and rowing.

Participants will be instructed to exhale while lifting a weight and inhale while lowering it, to minimize blood pressure excursions, and to rest for 2-3 min between sets. Participants will perform 1 set of resistance exercise 3 times weekly for the first 2 weeks, 4 sets of each resistance exercise 3 times weekly during weeks 3 and 4, and complete set of resistance exercise in the last 4 weeks. For each station, the participants will spend 10 min; this includes the substations. Resistance will be increased by 5-10 kg, once the participant is able to perform more than 15 repetitions while maintaining proper form.

All the aerobic activities of the circuit training will be performed on a cycle ergometer. Participants will be free to vary the machine used from one visit to the next. Exercise intensity will be standardized by using heart rate monitors (Polar Electro Oy) that will display the participant's heart rate and emit a warning signal if the heart rate goes outside the prescribed training zone, thus guiding the participant to adjust the workload up or down to achieve the desired intensity. In addition, the rate of perceived exertion will be measured using the Borg scale.

The Routine Care Group (Control Group)

Participants in the control group will receive routine medication as prescribed by the attending physicians at the diabetes clinic and will be monitored. Their prescriptions will be guided by the IDF guidelines. After 8 weeks of routine care, the participants will be enrolled into either the rebound exercise or circuit exercise group. The control group will be given health magazines to read, whereas the exercise groups will be engaged in the exercise programs.

All the 3 groups will receive routine medication and counseling regarding diet, weight control, and information to identify, minimize, or avoid complications of diabetes.

Measurement

The following measurement would be taken during the data collection they are as follows:

1. Sociodemographic variables: The sociodemographic variables of the participants will be recorded before the commencement of the study. These include age, race, gender, height, weight, educational level, duration of diabetes, level of pain, blood pressure, pulse rate, and heart rate.
2. Pain intensity: The alternate visual analog scale will be used to assess the pain level of the participants. The participants will be requested to rate on a 0-10 scale, the level of pain they felt 6 weeks before and at present. On the scale, 0 indicates no pain or no interference, whereas 10 is pain as bad as it could be/extreme interference [26]. The alternate visual analogue scale has been reported to have a high validity, increased patient compliance, greater sensitivity of measurement, and reduced bias [26].
3. BDI: This will be used to assess and screen participants for depression. The BDI is a 21-item multiple choice self-reported inventory, widely used to assess the presence and degree of depression in adolescents and adults [27]. The BDI is a self-administered questionnaire and it has a high test-retest reliability (Pearson *r*).
4. QoL: The General Health Survey Short Form (SF-36) will be used to measure changes in the participant's QoL. The instrument has shown good validity and reliability of Cronbach alpha of .85 and reliability coefficient of .75 for all the domains except social functioning [28]. The short form, SF-36, measures perceived health in the areas of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, with higher scores (range 0-100) reflecting better-perceived health.
5. Biochemical parameters: Fasting blood glucose in mmol/L, blood total cholesterol (TC) in mmol/L, low-density lipoprotein (LDL) mmol/L, very low-density lipoproteins (VLDL) mmol/L, and high-density lipoprotein (HDL) mmol/L will be determined at baseline and after 8 weeks of the program. A blood sample will be taken by pinprick using Accu-check Sofclix Pro Roche Diabetes care, South Africa. Then, the following parameters will be evaluated: fasting glucose level using Accutrend (Roche Diagnostics, GmbH Germany); HDL-C using PEG þ cholesterol oxidase (Roche Diagnostics GmbH Germany); triglycerides using glycerol phosphate-PAP (Roche Diagnostics GmbH Germany); and TC using cholesterol oxidase-PAP (Roche Diagnostics GmbH Germany) to evaluate TC, LDL, VLDL, and HDL-C.
6. Pulmonary parameters: Pulmonary function parameters will be measured at baseline and after the 8 weeks of the study using Spiro 232 (PK Morgan, India). The following parameters will be measured: Forced expiratory volume in first second (FEV_1) (lt), forced vital capacity (FVC), FEV_1/FVC ratio, peak expiratory flow rate, and maximal voluntary ventilation (lt/min). The spirometer will be connected to a computer that will record all the values.

Sample Size and Power Calculation

The sample size (N) will be determined using Cohen table [29] at alpha=.05 and degree of freedom (μ)=k−1, where k is the number of groups, with effect size f=0.35. From the previous study [17] and power (w) 80%, sample size n=20. Sample size (N) will be 60, and 12 extra participants will be added to make room for attrition. Therefore, the sample size will be 72 participants, and each group will be 24 participants.

Randomization and Blinding

Randomization will be conducted using a computer-generated random allocation sequence schedule conducted by a physiotherapist who is not involved in the research and has experience in research, who will randomly allocate recruited participants into the rebound exercise group, circuit training group, and the control group. To eliminate bias, the assessment of outcome will be performed by experienced assessors who will be blinded to the type of intervention as well as the intervention groups of the participants. Participants will also be instructed not to disclose their individual intervention groups to the assessors. Figure 1 shows the flow diagram.

Procedures

Assessment of participants will be conducted at 2 stages: at baseline and at the end of 8 weeks of intervention. To ensure a comprehensive assessment, a battery of measures was chosen covering the WHO-ICF model [30]. Certain tools were selected to cover the 3 key domains proposed by the ICF: body structures and function (hematological variables, MSKP, and respiratory parameters), activity, and participation (QoL and depression). At baseline, participants will be assessed for sociodemographic characteristics, which will include personal demographic information and diabetes-specific information. The personal demographic information will include age, sex, height, weight, marital status, educational qualification, and employment. The diabetes-specific information will include type of diabetes and duration since diagnosis. At the baseline, the outcome measures to be used for these assessments are presented in the measurement section. Table 1 shows the instruments.

Data Management

Data from the trial will be monitored by regularly scrutinizing data files for omissions and errors. All manually entered data will be double entered, and the source of any inconsistencies will be explored and resolved. Electronic data will be stored on password-protected servers at the Department of Physiotherapy, School of Health Sciences, University of KwaZulu-Natal, Durban, and written forms and data will be stored in locked filing cabinets at the Department of Physiotherapy, School of Health Sciences, University of KwaZulu-Natal, Durban. Data will only be accessible to the researcher. Each participant in the study will be provided with an identification number. All recorded data will be coded using this number.

Figure 1. CONSORT flow chart.
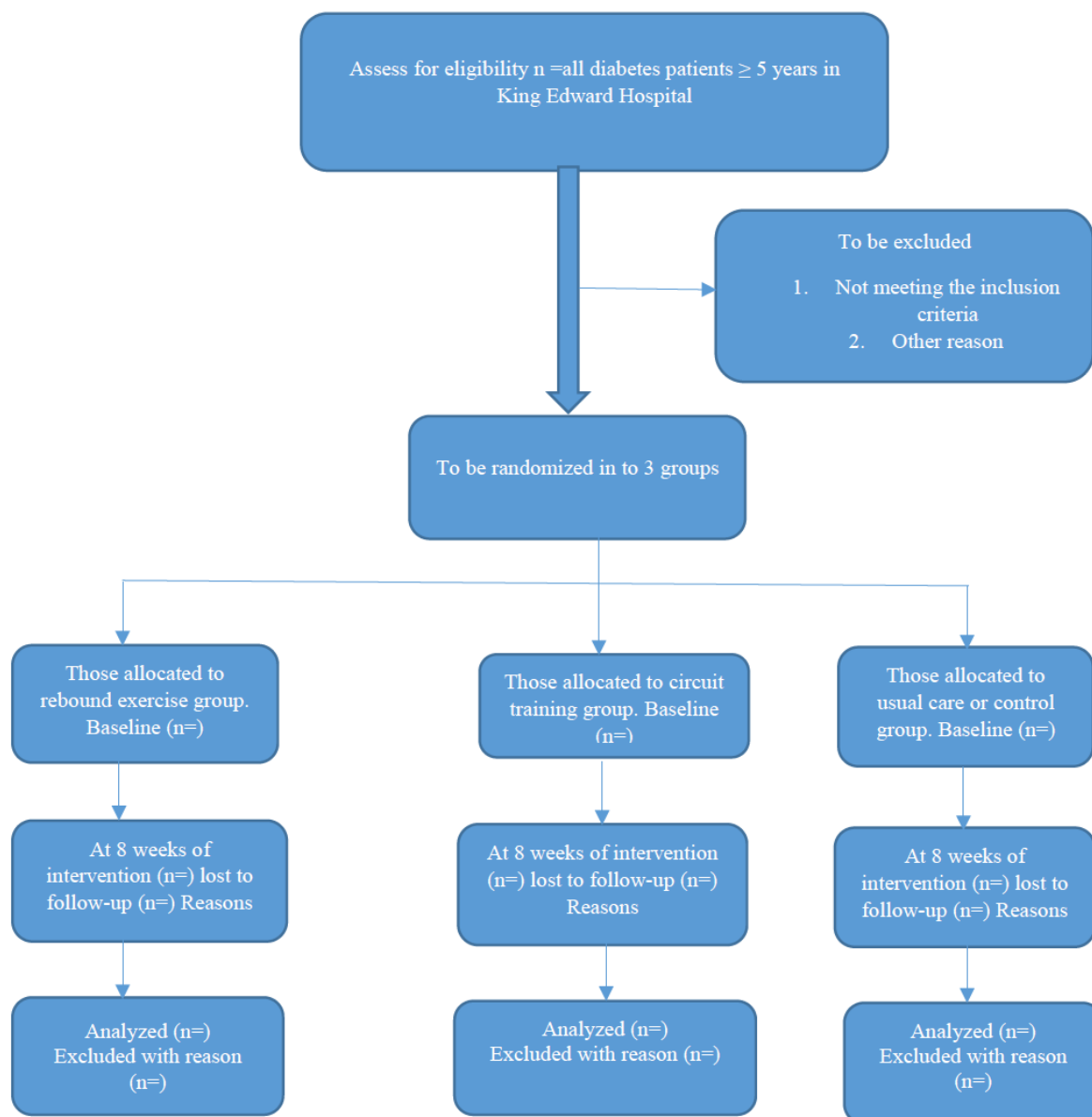
Table 1. Study assessment tools.

Scales or tools	Function or applications
Metronome	To provide signals for participants during exercises
Mini trampoline	For rebound exercise
Treadmill	For aerobic component of circuit training
Biodata form	To record the sociodemographic variables of participants
Alternate visual analog scale	To assess change in pain scores of participants
Beck Depression Inventory	To assess change in depression of participants
General health survey short form (SF-36)	To assess change in quality of life of participants
Accutrend plus	To assess the fasting glucose-level change and cholesterol-level change in participants
Spiro232	The spirometer will be used to measure change in forced expiratory volume, forced vital capacity, peak expiratory flow rate, and maximal voluntary ventilation

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Data Analysis

Preliminary analysis will be performed to test the normality of the data using the Kolmogorov V-Smirnov test before the analysis. Demographic data will be analyzed using descriptive statistics, whereas data on QoL and depression will be analyzed within the group using the Wilcoxon signed rank test and between the groups using the Kruskal-Wallis test. Post hoc test will be used for any significant F values.

The paired *t* test will be used within the group for pain scores, fasting glucose, and cholesterol level of the participants and between groups using 1-way multivariate analysis of variance. Post hoc test will be used for any significant F values. The level of significance will be set at .05. The SPSS version 23 will be used for the analysis.

Ethics and Informed Consent

Ethical approval was sought and obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee South Africa (BREC/BF/371/17) and registered with Clinicaltrials.gov: NCT03200795. Informed consent will also be obtained from the participants.

Results

The results of this study are expected to provide additional information on the effect of rebound exercise and circuit training in the management of patients with musculoskeletal complications of diabetes in South Africa. It is hoped that it will lead to improvement in the QoL, reduction in MSKP and depression, improvement in glycemic control, reduction in cholesterol level, as well as improvement in respiratory capacity of type 2 diabetes patients. It is also expected to give information about which of the exercises is most effective in the management of patients with musculoskeletal diabetes complications in terms of pain relief, glycemic control, cholesterol level, improvement in QoL, level of depression, and respiratory capacity.

Discussion

Though different additional strategies such as exercise and dietary and lifestyle modifications exist for the control of type 2 diabetes, they are mostly applied for the control of glucose level. No strategies have been identified for the control of complications associated with diabetes such as MSKP, depression, and reduction in the QoL. To date no additional rehabilitation [31] that is aimed at alleviating MSKP associated with diabetes complication. Exercises in the management of type 2 DM are of different type of different modes and intensity, most of the exercises are aerobic in nature and involves weight bearing, and strength training, mostly targeted for glycemic control, cholesterol, and few in QoL.

Exercises that are nonweight bearing, such as rebound exercises, and that require less equipment are used in the management of type 2 diabetes [23]. Studies on rebound exercises mostly focus on the glycemic control and change in cholesterol level. This trial is focused on the effect of exercises such as rebound exercise on respiratory parameters, MSKP, and QoL. The current literature suggests that emphasis in any current trial in the management of type 2 DM should focus on QoL, respiratory capacity, and psychosocial variables [32-34]. Moreover, if studies on exercises among patients with diabetes focus on respiratory and musculoskeletal complications, they are likely to result in improved functions and reduce complications.

The possible limitation of this protocol is that it is limited to the short-term effect. It is hoped that subsequent trials will look into the long-term effect of both rebound exercise and circuit training in the management of MSKP associated with diabetes.

Conflicts of Interest

None declared.

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Abbreviations

BDI: Beck Depression Inventory
DM: diabetes mellitus
FEV: forced expiratory volume
FVC: forced vital capacity
HDL: high-density lipoprotein
ICF: International Classification of Functioning Disability and Health
IDF: International Diabetes Federation
LDL: low-density lipoprotein
MSKP: musculoskeletal pain
6MWT: 6 min walk test
QoL: quality of life
RCT: randomized controlled trial
SF-36: short form 36
VLDL: very low-density lipoprotein

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Proposal

The Detroit Young Adult Asthma Project: Proposal for a Multicomponent Technology Intervention for African American Emerging Adults With Asthma

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Abstract

Background: Racial and ethnic minority youth have poorer asthma status than white youth, even after controlling for socioeconomic variables. Proper use of asthma controller medications is critical in reducing asthma mortality and morbidity. The clinical consequences of poor asthma management include increased illness complications, excessive functional morbidity, and fatal asthma attacks. There are significant limitations in research on interventions to improve asthma management in racial minority populations, particularly minority adolescents and young adults, although illness management tends to deteriorate after adolescence during emerging adulthood, the unique developmental period beyond adolescence but before adulthood.

Objective: The objective of the pilot study was to test the feasibility, acceptability, and signals of efficacy of an intervention targeting adherence to controller medication in African American youth (ages 18-29) with asthma. All elements of the protocol were piloted in a National Heart, Lung, and Blood Institute (NHLBI)–funded pilot study (1R34HL107664 MacDonell). Results suggested feasibility and acceptability of the protocol as well as proof of concept. We are now ready to test the intervention in a larger randomized clinical trial.

Methods: The proposed study will include 192 African American emerging adults with moderate to severe persistent asthma and low controller medication adherence recruited from clinic, emergency department, and community settings. Half of the sample will be randomized to receive a multicomponent technology-based intervention targeting adherence to daily controller medication. The multicomponent technology-based intervention consists of 2 components: (1) 2 sessions of computer-delivered motivational interviewing targeting medication adherence and (2) individualized text messaging focused on medication adherence between the sessions. Text messages will be individualized based on ecological momentary assessment. The remaining participants will complete a series of computer-delivered asthma education modules matched for length, location, and method of delivery of the intervention session. Control participants will also receive text messages between intervention sessions. Message content will be the same for all control participants and contain general facts about asthma (not tailored).

Results: It is hypothesized that youth randomized to multicomponent technology-based intervention will show improvements in medication adherence (primary outcome) and asthma control (secondary outcome) compared with comparison condition at all postintervention follow-ups (3, 6, 9, and 12 months). The proposed study was funded by NHLBI from September 1, 2016 through August 31, 2021.

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Conclusions: This project will test a brief, technology-based intervention specifically targeting adherence to asthma controller medications in an under-researched population, African American emerging adults. If successful, our multicomponent technology-based intervention aimed at improving adherence to asthma medications has the potential to improve quality of life of minority emerging adults with asthma at relatively low cost. It could eventually be integrated into clinical settings and practice to reach a large number of emerging adults with asthma.

Trial Registration: ClinicalTrials.gov NCT03121157; https://clinicaltrials.gov/ct2/show/NCT03121157 (Archived by WebCite at http://www.webcitation.org/6wq4yWHPv)

Introduction

Background

Asthma disproportionately affects underrepresented minority populations, with African Americans having higher rates and poorer asthma outcomes than other racial and ethnic groups [1,2]. Despite growing awareness of these inequities, disparities in asthma rates and outcomes persist [3]. Age-related (or developmental) inequities also exist within minority populations, as African American adolescents and young adults have poorer asthma outcomes and higher asthma mortality rates than African American adults [2,4-8]. Overall, racial and ethnic minority youth have poorer asthma outcomes than white youth, even after controlling for socioeconomic variables [9], which may be due, in part, to differences in self-management. For example, African Americans and Latinos report low use of controller medications [9,10], often use a "crisis management style over-relying on rescue medications [10], and are nonadherent to treatment plans [10]. Proper use of medications is critical in reducing asthma mortality and morbidity [11-13]. Clinical consequences of poor asthma management include increased illness complications, excessive functional morbidity, and fatal asthma attacks [14,15].

This project focuses on African Americans in *emerging adulthood*, a unique developmental period (age 18-29 years) beyond adolescence but before adulthood [16] largely neglected in research. This represents a significant gap in knowledge, given emerging adults are at increased risk for illness consequences, even more so than adolescents. The necessary transition to adult care settings can be difficult for those with chronic conditions [17-20]. Aging out of pediatric care is often associated with increased risk for problem behaviors such as homelessness and substance abuse [17] and overreliance on the emergency room for health care [21]. Emerging adults with asthma are less likely to have a usual source of health care and more likely to visit the emergency department (ED) than older adolescents with asthma [22]. The transition to adult care can be abrupt and can occur with little preparation because age, rather than developmental maturity, triggers the transition. Given these barriers, it is not surprising that illness management deteriorates during emerging adulthood [18,23,24]. The research literature on interventions to improve asthma management is nearly nonexistent in emerging adults [25-27]. Results of studies with minority adults suggest that programs that target even just 1 or 2 aspects of asthma management (eg, adherence to

medications) have largely been successful [28]. Thus, targeted interventions may have promise for improving morbidity and mortality rates in minority youth at highest risk for poor adherence and health outcomes. However, successful interventions must consider the target group's distinctive developmental needs and unique culture [29]. This project tests a developmentally and culturally appropriate intervention for urban African American emerging adults (aged 18-29 years) with persistent asthma and poor adherence.

"eHealth," "mHealth," "telemedicine," and "telehealth" have become buzzwords for the use of electronic information and mobile communication technology in health care and behavioral health [30,31]. Technology-based interventions cannot replicate the important human elements of traditional interventions. However, technology offers tremendous advantages in terms of reach, cost, anonymity, and time. We have developed and pilot tested a multicomponent, technology-based intervention (MCTI) specifically targeting adherence to controller medication in African American emerging adults that integrates 2 powerful technologies for behavior change—interactive computer-delivered intervention sessions and text messaging reminders between sessions. Each of these components is also tailored via text messaging based on an assessment of each participant's experiences living with asthma. This method of data collection is called ecological momentary assessment or "EMA" [32]. EMA refers to a set of methods that allow a research participant to report on symptoms, affect, behavior, and cognitions in "real time" rather than rely on more traditional retrospective self-reporting such as with a questionnaire or interview [32]. Despite the rapid growth of technology in behavioral health, we know of no other published technology-based interventions that have specifically targeted African American emerging adults with asthma or any other chronic illness. We also are not aware of any other programs that have integrated multiple technologies for assessment, intervention, and intervention tailoring, which represent a major limitation, given that technology-delivered interventions for adults living with asthma generally have favorable results for asthma management and knowledge [33-36]. Technology-based interventions may be particularly well-suited for youth, including emerging adults, because they tend to use computers, cell phones, and text messaging so frequently in their daily lives [37-41]. Emerging adults, including urban minority youth, also tend to use multiple sources of technology.[42].

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Motivational interviewing (MI) is a collaborative, goal-oriented style of communication with particular attention to the language of change. It is designed to strengthen personal motivation for and commitment to a specific goal by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion [43]. The theory underlying MI is consistent with evidence from other psychotherapy outcome research, which indicates that factors such as empathy, optimism, and congruence are strongly linked to client outcome [44]. Originally developed for use with substance abusers, MI adaptations for youth with other chronic conditions have shown strong effects for this brief intervention approach [45-49], and 1 meta-analysis suggested stronger effects in studies targeting minority populations [50]. MI is consistent with several models of health behavior change, including the information-motivation-behavioral (IMB) skills model that serves as the foundation of the current intervention [51]. Importantly, 1 common shortcoming of Internet-based behavior change interventions for asthma is lack of foundation in a theoretical model [52]. According to the IMB model, behavior change results from the joint function of 3 critical components: accurate information about risk behaviors (eg, risks of not taking asthma medications as prescribed) or their replacement health behaviors (eg, benefits of taking asthma medications), the motivation to change behavior, and the perceived behavioral skills necessary to perform the behavior (eg, self-efficacy). Thus, the intervention is intended to improve medication adherence behavior by targeting motivation and providing information about asthma management in an MI-consistent way. Furthermore, text messaging reminders promote the translation of information and motivation into behavior skills as they prompt the youth in real time about their plans for changing asthma management behavior. Overall, MI has been shown to hold great promise in promoting behavior and attitude change in people with health difficulties. However, one of the key issues when considering using MI in health settings is the amount of training that might be required for health professionals to use MI and whether implementing MI can fit within the demands of busy health settings [53]. The MCTI uses computer-delivered MI, which may offer some practical and logistical advantages over traditional person-to-person therapeutic delivery in busy health settings.

The purpose of this proposal was to test a brief MCTI, rigorously developed through a rigorous, multistep process with pilot funding from National Heart, Lung, and Blood Institute (NHLBI) to improve asthma controller medication adherence in urban African American emerging adults [54-57]. The MCTI is based on the IMB skills model, MI strategies, and EMA. The proposed project includes significant innovations that go beyond the current state of eHealth interventions by (1) using multiple technologies to extend the reach of the intervention and (2) individualizing the intervention for each participant through real-time assessment of his or her experiences living with asthma through EMA. All elements of the proposed study protocol were piloted in NHLBI R34 (1R34HL107664 MacDonell). Results suggested feasibility and acceptability of the study protocol as well as proof of concept in a pilot randomized clinical trial [55]. We are now ready to test the intervention in a randomized clinical trial. The proposed study will include 192 African American emerging adults with moderate to severe persistent asthma and low controller medication adherence recruited from clinic and ED settings. Half of the sample will be randomized to receive an MCTI targeting adherence to controller medication. The MCTI consists of 2 components: (1) 2 sessions of computer-delivered MI targeting medication adherence and (2) individualized text messaging focused on medication adherence between the sessions. At study start, participants receive 7 days of "real-time" data collection via text messaging (EMA) and daily diary. Data are collected on daily controller medication adherence, asthma symptoms, and barriers to asthma management and are used to tailor the intervention for each participant. The remaining half of participants (control group) will complete a series of computer-delivered asthma education modules matched for length and method of delivery of the intervention session. Control participants will also receive text messages between intervention sessions. Message content will be the same for all control participants and contain general facts about asthma. Youth will be recruited from the Detroit Medical Center, the only university-affiliated medical center in Detroit, Michigan. Detroit is an appropriate setting for this work as it has the highest percentage of African Americans of any major city in the United States. A 2013 report of the Michigan Department of Community Health found that asthma prevalence and asthma-related deaths in Michigan are above the national average and occur disproportionately in Wayne County where Detroit is located.

Study Aims

Primary Aim

The primary aim of this study was to test the efficacy of a 2-session MCTI to improve controller medication adherence (primary outcome) and asthma control (secondary outcome) in African American emerging adults (aged 18-29 years) with poorly controlled asthma and low medication adherence.

Secondary Aim

The secondary aim of this study was to identify the mechanisms (mediators) of MCTI treatment effects on primary outcomes. Proposed mediators through which MCTI will exert its effects are derived from the IMB skills model: asthma treatment knowledge, self-efficacy, and motivation for adherence.

Methods

Study Overview

Participants will be randomized (1:1) to an MCTI targeting asthma medication adherence or to a comparison control condition. A repeated measures design (baseline and 1-, 3-, 6-, 9-, and 12-months postbaseline) will be used with the primary outcome being adherence to daily controller medications and the secondary outcome as asthma control. We expand on the pilot study [55] by testing the long-term effects over 1 year, which allows us to account for seasonal variability of symptoms in a young, urban population [58,59], to gain understanding of the long-term impact on adherence behavior, and to allow trajectory analyses of adherence.

Overview of Multicomponent Technology-Based Intervention

The MCTI was tested in a pilot randomized controlled trial [54,60] and is an integration of several technology-based components. The intervention group will receive 2 sessions of computer-delivered MI via CIAS software (Interva, Detroit, MI) programmed to target adherence to medications. The intervention group will also receive text messaging adherence reminders between sessions. Both the computer-delivered sessions and text messages will be tailored to the participant using EMA.

Sessions are provided by an animated character (avatar, eg, "Peedy" the parrot). The participant picks their preferred character from 10 possible choices at the start of the session. All avatars were developed via focus groups with African Americans. Significant efforts have been made to ensure that the animated character delivers the intervention in a way that has high fidelity with the most recent edition of Motivational Interviewing (MI-3) [43]. MI-3 is specified by 4 processes: (1) engaging, (2) focusing, (3) evoking, and (4) planning. The intervention engages the youth with the avatar's communication of empathy, optimism, and autonomy support. The intervention focuses the youth on adherence and relevant health behaviors with feedback on adherence, asthma symptoms, and tailored education. The avatar evokes both importance and confidence (key components of readiness or motivation) with MI strategies such as identifying pros of behavior change, affirmations to reinforce change talk and boost confidence, and identification of strengths and resources. The intervention also manages counter-change talk by having the avatar reflect without judgment and provide statements to emphasize autonomy. Finally, participants are guided in the planning process through goal-setting activities. Importantly, as with a face-to-face interaction with a human counselor, the interactions between the computer-delivered motivational intervention and the participant are synchronous and not reliant on feedback at the completion of the session. Small amounts of appropriate psychoeducation about potential improvements in asthma health outcomes that can result from improvements in asthma regimen adherence are integrated with the more purely motivational elements of the intervention. The provision of such information is consistent with the IMB model, which suggests that motivational approaches are most effective in the context of sensitively provided information about a health-related behavior [51], such as adherence. The length of the intervention sessions is about 30 min each, with the total duration of the visit (assessment and intervention) lasting about 1.5 hours.

Participants receive daily text messaging between the intervention sessions. The message timing and content are individualized based on EMA as well as participant response to the intervention. Those participants who indicate that they are "ready" to set the goal to take their medications as prescribed will receive text messages to remind them to take their medications. Those who indicate that they are less than ready (ranging from "not at all ready" to "somewhat ready") to try and take their medications as prescribed can choose from a range of alternatives, including taking medications at least 50% of the time, to just think about taking medications, or to opt out

of text messages and considering medications entirely. Text messaging content and timing for those who are not ready to take their medications are individualized based on the participant's choice, ie, those who do not receive adherence reminders receive a daily message encouraging them to work toward their chosen goal.

The MCTI is tailored for each participant in several ways: (1) the computer-delivered intervention is an interactive program that is individualized based on MI principles, (2) participants in the intervention condition receive personalized feedback during the computer-delivered intervention sessions based on their recent asthma symptoms and medication use, and (3) text messages received between intervention sessions are tailored based on the medication routines and readiness to take medications as described by the participant.

Control Condition

Effective comparison conditions must (1) include aspects or processes of treatment shared in common by behavioral interventions, (2) avoid processes specific to the experimental intervention, (3) avoid processes specific to other existing interventions, and (4) be credible enough to generate participant interest [61]. Control participants complete CIAS-delivered (Interva, Detroit, MI) asthma education modules matched for length, location, and method of delivery of the intervention session. These modules were created using content from the Asthma and Allergy Foundation of America and focus on facts and myths about asthma, controlling environmental factors such as asthma triggers, and pharmacologic management. Module content is consistent with the National Asthma Education and Prevention Program *2007 Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Control participants complete each module at their own pace and then complete a short quiz to assess their knowledge. Control participants also receive text messages between intervention sessions. Message content is the same for all control participants and contains general facts about asthma (not tailored). Messages timing is not tailored and is sent at the same time every day (4:00 PM—time chosen to avoid AM and PM medication times but not to interfere with sleep and school activities). This comparison condition controls for improvement because of nonspecific intervention factors such as positive expectancies due to entering treatment, positive regard and attention from being part of the intervention project, and having opportunities to learn about asthma and asthma treatment and matching for dose (EMA assessment, 2 sessions of software interaction, and daily text messages).

Participants and Recruitment

The study will include 192 African Americans (aged 18-29 years) with moderate to severe persistent asthma requiring daily controller medications. We define persistent asthma according to 2007 NHLBI guidelines: level of symptoms, as defined by any of the following in the last 4 weeks: (1) use of any asthma medication more than 2 times a week; (2) daytime asthma symptoms such as wheezing, tightness of chest, coughing more than 2 times week, or waking up at night because of asthma more than 2 times a month. To be eligible, patients must report poor adherence to daily controller medications during eligibility

screening. Poor adherence is defined as not taking medications "as prescribed" less than 80% of the time. This definition of underuse is consistent with previous work focused on underuse of asthma controller medications in children and adults. Participants must also live in the Detroit area (within 30 miles) and be able to complete questionnaires in English. Participants must also own or have access to a cellular phone for the duration of the study. We had no potential participants excluded because they lacked a cell phone with text messaging; moreover, nearly all had cell phone plans with unlimited texting. Thus, we expect few exclusions related to cell phone ownership. No exclusions will be made because of comorbid mental health problems (ie, attention-deficit/hyperactivity disorder depression), except thought disorder (ie, schizophrenia, autism), suicidality, or mental retardation. It is assumed that severe psychosis or suicidality may require management beyond the scope of our interventions. Youth with other chronic health conditions requiring ongoing medical intervention (eg, HIV, type II diabetes) will be excluded. Youth who have previously participated in our feasibility trials or pilot will also be excluded.

The proposed project will utilize the resources of the Department of Family Medicine, Clinical Research Service Center (CRSC), and Integrative Biosciences Center at Wayne State for recruitment, implementation, and retention. These centers have well-established recruitment and consenting practices; moreover, much effort went into streamlining our recruitment and consenting procedures during the R34 pilot. Health Insurance Portability and Accountability Act privacy practices require that contact regarding the study be made first by medical staff. We piloted recruitment procedures at multiple primary care and emergency care sites and have selected two for the randomized controlled trial: Detroit Medical Center Internal Medicine and emergency departments (EDs; Detroit Receiving Hospital and Sinai Grace). These sites were those where we actually found emerging adults in care for asthma or nonasthma-related issues. For recruitment in the ED, Clinical Research Service Center staff will recruit, preliminary screen, and obtain an authorization to contact form. Patients may be prescribed a controller medication and/or refill of medication(s) upon discharge of the ED, as is standard practice. In the internal medicine/ambulatory clinics, medical staff will screen and obtain an authorization to contact form. To expand our reach and enrollment, we are adding an additional ED site (Harper at Detroit Medical Center), several more federally-qualified health centers, and community/online recruitment approaches. Regardless of recruitment source, participants will be screened by a research assistant and consent using an in-person, written informed consent prior to enrollment and study entry.

Procedures

All data collection and sessions will take place at clinic research space at Wayne State University iBio or in a private place (eg, the participant's home). Data collection is conducted on the laptop computer with each questionnaire item read to the participant by the computer (headphones are provided for privacy). However, a human data collector is also present during the session to explain and demonstrate computer usage and troubleshoot any difficulties. Data collection occurs at baseline and at 1, 3, 6, 9, and 12 months, with intervention sessions at 1 week postbaseline and concurrent with the 1-month data collection. The 9-month assessment is limited and over the phone to reduce burden. Data collection includes measurement of pulmonary functioning, EMA, and computer-delivered questionnaires (CIAS). EMA is collected via daily text messaging and diaries before the computer-delivered sessions at baseline and at 3, 6, and 12 months. The Doser is attached to the primary MDI at baseline and at 6 and 12 months at the start of EMA and removed after each EMA period. We do not include EMA or Doser at every session to minimize participant burden (9-month follow-up is only CIAS (Interva, Detroit, MI), and data collection via phone call and EMA/Doser are staggered).

All sessions (including combined assessment or intervention session) will take less than 1.5 hours to complete (we reduced number of questionnaires based on participant feedback). Participants will be randomized following the baseline session. For the intervention group, the intervention authoring ability is built on top, so responses to assessment questions feed directly into the intervention to begin the intervention tailoring. Control group participants receive the same questionnaires, EMA, and pulmonary functioning assessment for data collection followed by computer-delivered asthma education matched for length of time of the intervention. Because the assessment is computer administered, there is no data collection staff per se for written measures. Research staff responsible for recruitment and retention will be blind to treatment status to the extent possible in a behavioral trial. The software will randomly assign participants to conditions in a 1:1 ratio and notifies the participants of their randomization status. To minimize attrition, we will use approaches that have been successful in our studies in retaining urban, minority samples such as keeping in regular contact with participants via letters, calls, and texts, requesting alternate contacts in case phone numbers change, and so forth.

Measures are collected at baseline and at 1, 3, 6, 9, and 12 months (see Table 1). Psychological distress and demographics are collected only at baseline. Pulmonary function testing (PFT) and Doser are collected at baseline and at 6 and 12 months. EMA is not obtained at 1 month because of study design or at 9 months to reduce participant burden. All measures have been found to be reliable and valid.

Table 1. Primary and secondary outcome measures. EMA: ecological momentary assessment; IMB: information-motivation-behavioral.

Measure	Description of measure
Primary outcome: medication adherence	
Medication adherence (EMA)	Text messages daily to prompt for adherence to controller medication. Participants will also complete a diary at the end of each day to assess asthma symptoms and barriers.
Medication adherence [62] (written measure)	12-item, yes/no response measure asks about controller medication use in the last 3 months (Have you forgotten to take medications as prescribed, etc.).
Medication adherence (objective measure) [63]	A Doser tracking device will be used (with covert display mode) to measure number of doses during the EMA period at baseline and at 6 and 12 months [64]. Prompts have been added to check that devices are attached and functional.
Secondary outcome: asthma control	
Asthma symptoms (EMA)	Text messages daily to prompt for asthma symptoms and a text each morning to ask for total symptoms experienced the previous day and night. Participants also complete a diary at the end of each day to assess mood and impact of asthma on activity level and daily life.
Asthma Control Test (ACT) [65]	A 5-item questionnaire. Scores range from 5 (poor control of asthma) to 25 (complete control of asthma), with higher scores indicating greater asthma control. An ACT score >19 indicates well-controlled asthma.
Pulmonary functioning	Forced expiratory maneuvers (forced expiratory volume in 1 second and forced viral capacity) will be obtained with a calibrated recording spirometer (KoKo portable device) at baseline, and at 6 and 12 months.
Proposed mediators	
Asthma Knowledge, Attitudes, and Self-Efficacy Questionnaire (KASE-AQ) [66]	60 items, using a Likert scale response set, assess knowledge regarding asthma, their attitudes about their asthma, and their self-efficacy regarding their perceived ability to control their asthma consistent with the IMB skills model.
Motivation for adherence	Internal and external motivation for asthma medication adherence will be measured consistent with the IMB skills model.
Baseline descriptive measures	
Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) [67]	The ASSIST was developed for the World Health Organization to detect psychoactive substance use and related problems in primary care patients. Only tobacco and marijuana use will be assessed.
Brief Symptom Inventory (BSI) [68]	The BSI-18 measures psychological distress (anxiety, depression, and somatic complaints).
Participant satisfaction	
Client satisfaction	Participants will complete a brief satisfaction questionnaire at the end of session 2.

Statistical Analyses

The intervention effect will be assessed in 3 steps. First, assess comparability of the intervention and control condition. Despite random sampling, participants in the actual sample may not always be comparable. Baseline differences in mean scores of medication adherence and asthma control and demographic characteristics (eg, age, gender, and race) and attrition to follow-up between the intervention and control groups will be examined using chi-square test (for categorical variables) and analysis of variance (for continuous variables). Variables that significantly differ between intervention and control groups will be used as covariates in multivariate analysis. Second, bivariate analyses will be used to assess potential differences between intervention and control groups on outcome measures (medication adherence and asthma control measured as a count variable) at baseline and each follow-up. To examine the effect of the intervention on these outcomes, we compared the difference in medication adherence and asthma control between the intervention and control groups using Wilcoxon rank-sum test (instead of t test), as these outcomes are usually non-normally distributed. Asthma control will be further categorized into "well-controlled" versus "poorly controlled" asthma. The difference in the proportion of "well-controlled" asthma between the intervention and control groups will be assessed using chi-square test. The difference in proportion of "well-controlled" asthma between baseline and follow-up visits within each study group will be examined using McNemar test. Finally, significant findings will be verified using a multivariate approach. The intervention effect on medication adherence and asthma control will be further assessed using mixed-effects modeling, controlling for potential confounding factors (eg, age, race, gender, and intervention sites), possible baseline differences in outcome measures, and the clustering effects of repeated measurements. To use the mixed-effect modeling analysis in assessing intervention effect, an interaction term (intervention group by time) will be included together with other covariates. A significant beta coefficient of the interaction term at $P<.05$ level will be used as evidence supporting the intervention effect.

Specifically, mixed-effects models using PROC MIXED SAS procedure will be conducted to examine the intervention effect on medication adherence and asthma control. For asthma control outcome ("well-controlled" vs "poorly controlled" asthma), we will also conduct generalized mixed models (PROC GLIMMIX). Missing data (missing at random) are handled using full information maximum likelihood estimation in these mixed-effect models. If data are not missing at random, we will conduct a sensitivity analysis, which allows us to investigate possible violations of the missing data at random assumption. When the amount of missing data is large (25%), which is very unlikely to occur based on our data collection experience in the previous R34 grant, we may consider the last observation carried forward method in the longitudinal data analysis. All the analyses will be conducted using SAS 9.4 statistical software package.

Structural equation modeling (SEM) will be used to examine the extent to which the targeted variables (eg, IMB skills) mediate the intervention effect. The purpose is to provide further evidence supporting the theory-based intervention. The analysis plan expands on the procedures outlined by Baron and Kenny [69], making use of causal modeling. Simple correlation and path models will be used first to explore variables that may mediate the intervention on outcome measures. SEM models will thus be constructed based on results from the simple analysis. To build a parsimonious SEM mediation model, empirical Bayes estimates of intra-individual change will be estimated for both mediating constructs and outcome variables. SEM analysis will be performed with the software M-Plus. The model will be evaluated using several model fit indices, including standardized root mean square residual (SRMR), comparative fit index, and root mean square error of approximation (RMSEA). Values for the SRMR range from 0 to 1 with well-fitting models obtaining values less than .05 [70,71]. For comparative fit index, a cutoff criterion of ≥.95 will be used as indicative of good fit [72]. For RMSEA,.01, .05, and .08 will be used to indicate excellent, good, and mediocre fit, respectively [73].

It is critical to understand who responds to a brief intervention and who might require more intensive treatment. We will use developmental trajectory analysis to explore subgroups of participants with similar adherence and control trajectories over 12 months. This approach is preferable to a priori specifying the type or number of trajectories or relying on ad hoc categorization and has been recently applied to understanding clinical trials outcomes with children and adolescents. Some studies use only 2 trajectories of response and nonresponse and some find more (eg, improvers, slow improvers, relapsers, and responders). We will then use logistic regression to assess demographic and hypothesized predictors of treatment response (substance use, mental health, barriers, treatment site, and engagement in health care). Binary logistic regression may be used for 2 trajectories or to compare the most improved or least improved with others, whereas multinomial logistic regression may be used to compare multiple trajectories.

Potential Problems and Alternative Strategies

Differential loss to follow-up is a threat to internal validity to assess the effect of an intervention program. Possible barriers to project completion are high rates of no-shows at clinic visits or refusals to participate during ED recruitment, which would interfere with study recruitment and retention. Recruitment procedures and strategies were a primary focus of the R34-funded pilot, as we recognize that this population can be difficult to find in care and to recruit. In addition, we have strong collaborations in place through the Clinical Research Service Center and nurse recruiter to ensure recruitment success. Another possible issue is retaining youth in the study for the extended period (12 months). Multiple techniques are used to increase the likelihood that participants will keep their data collection appointments, including advanced scheduling, multiple reminder letters, and phone reminders. We piloted successful procedures and strategies for recruitment and retention during our pilot work, and our research center has a strong history of successful work with at-risk urban populations. We were also able to retain youth from 1- to 3-month follow-ups (with no activity between these data collections) and to have them initiate 3-month EMA without a face-to-face data collection. For the proposed trial, we will be seeing participants face-to-face to attach the Doser device at the start of the EMA period, which we anticipate will help ensure continued participation. Participants who do not complete intervention or control sessions will still be asked to provide follow-up data. When follow-up data are not available, the mixed model approach will use maximum likelihood estimates and all available data so no participants would be excluded. Thus, the intent-to-treat analyses will include all randomized participants, regardless of the intervention dose delivered. If missing data are not related to the outcome measures (missing at random), we will impute the missing data using advanced methodology [74]. Threats to internal validity of the study also may arise without sufficient attention to quality assurance of data collection and intervention delivery. Possible technological difficulties with the software, text messaging, or the server is another concern. Although these problems were minimal and remediated in the pilot study, we now have specific protocols and budget for technical support.

Results

The research protocol R01HL133506 (MacDonell) was funded by the NHLBI for the period September 1, 2016, through August 31, 2021. Notice of award was received on November 4, 2016. Enrollment began in June 2017 and will continue through February 2020. As of April 2018, 41 participants have been consented and enrolled. The final proposed sample is N=192.

Discussion

Youth randomized to the MCTI will show significantly greater improvements from baseline to postintervention in adherence as assessed by (1) self-reported doses missed, daily medication adherence (EMA), and monitoring using an adherence tracking device and (2) asthma control as assessed by symptom frequency from EMA and lung functioning (forced expiratory volume in

1 second) than youth randomized to the control condition delivered by the same platform and matched for dose.

Older adolescents and young adults have largely been ignored in the asthma intervention literature, although they are at highest risk for poor illness management and health outcomes. This project will test a brief, technology-based intervention specifically targeting adherence to asthma controller medications in an under-researched population, urban African American emerging adults. If successful, our MCTI aimed at improving adherence to asthma medications has the potential to improve quality of life of minority emerging adults with asthma at relatively low cost. Furthermore, it could be eventually be integrated into clinical settings and practice to reach a large number of emerging adults with asthma.

Conflicts of Interest

None declared.

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Abbreviations

ACT: Asthma Control Test
ASSIST: Alcohol, Smoking, and Substance Involvement Screening Test
BSI: Brief Symptom Inventory
ED: emergency department
EMA: ecological momentary assessment
IMB: information-motivation-behavioral
MCTI: multicomponent technology-based intervention
MI: motivational interviewing
RMSEA: root mean square error of approximation
SEM: structural equation modeling
SRMR: standardized root mean square residual

Protocol

Effectiveness of a Blended Multidisciplinary Intervention for Patients with Moderate Medically Unexplained Physical Symptoms (PARASOL): Protocol for a Cluster Randomized Clinical Trial

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Abstract

Background: Medically unexplained physical symptoms are an important health problem in primary care, with a spectrum from mild to chronic. The burden of chronic medically unexplained physical symptoms is substantial for patients, health care professionals, and society. Therefore, early identification of patients with moderate medically unexplained physical symptoms is needed in order to prevent chronicity. The preventive screening of medically unexplained physical symptoms (PRESUME) screening method was developed using data from the electronic medical record of the patients' general practitioner and demonstrated its prognostic accuracy to identify patients with moderate medically unexplained physical symptoms. In the next step, we developed a proactive blended and integrated mental health and physical therapy intervention program (PARASOL) to reduce complaints of moderate medically unexplained physical symptoms, stimulate self-management, and prevent chronicity.

Objective: The primary objective of this study is to investigate the effectiveness of the blended PARASOL intervention on the impact of symptoms and quality of life in patients with moderate medically unexplained physical symptoms compared with usual care. Secondary objectives are to study the effect on severity of physical and psychosocial symptoms, general health, physical behavior, illness perception, and self-efficacy in patients with moderate medically unexplained physical symptoms as well as to determine the cost-effectiveness of the program.

Methods: This paper presents the study protocol of a multicenter cluster randomized clinical trial. Adult patients with moderate medically unexplained physical symptoms will be identified from electronic medical record data using the PRESUME screening method and proactively recruited for participation in the study. Cluster randomization will be performed at the level of the participating health care centers. In total 248 patients with moderate medically unexplained physical symptoms (124 patients per arm) are needed. The PARASOL intervention is a 12-week blended primary care program consisting of 4 face-to-face consultations with the mental health nurse and 5 physical therapy sessions, supplemented with a Web-based program. The Web-based program contains (1) information modules and videos on self-management and educative themes, (2) videos and instructions on prescribed home exercises, and (3) assignments to gradually increase the physical activity. The program is directed at patients' perception of symptoms as well as modifiable prognostic risk factors for chronicity using therapeutic neuroscience education. It encourages self-management, as well as an active lifestyle using a cognitive behavioral approach and graded activity. Primary outcomes are impact of symptoms and quality of life. Secondary outcomes are severity of physical and psychosocial symptoms, general health, physical behavior, illness perceptions, self-efficacy, and cost-effectiveness. All measurements will be performed at baseline, 3

and 12 months after baseline. Retrospective cost questionnaires will also be sent at 6 and 9 months after baseline and these will be used for the cost-effectiveness analysis.

Results: The intervention has been developed, and the physical therapists and mental health nurses in the participating experimental health care centers have received two days of training on the content of the blended PARASOL intervention. The recruitment of health care centers started in June 2016 and inclusion of patients began in March 2017. Follow-up assessments of patients are expected to be completed in March 2019.

Conclusions: This study is the first randomized clinical trial to determine the effectiveness (including cost-effectiveness) of a proactive, blended, and integrated mental health and physical therapy care program for patients with moderate medically unexplained physical symptoms. The findings will help to improve the treatment for patients with moderate medically unexplained physical symptoms and prevent chronicity.

Trial Registration: Netherlands Trial Register NTR6755; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6755 (Archived by WebCite at http://www.webcitation.org/6ywporY7u).

Introduction

Medically unexplained physical symptoms (MUPS), especially pain, dizziness, and fatigue are frequent in primary care, in fact 25%-50% of all symptoms presented during consultations cannot be adequately medically explained [1]. If there are physical complaints for which no medical condition can be found after adequate medical examination, they will be defined as MUPS [2,3].

MUPS can be regarded as a spectrum ranging from mild unexplained physical symptoms (low incidence, one or two domains, low impact), to moderate symptoms (more frequent, two or three domains, higher impact) and finally to persisting or chronic MUPS (high impact, more clusters involved, chronic; eg, fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome) [3,4]. In this spectrum, mild MUPS have an estimated prevalence of 70% to 80% [4,5]. These patients consult their general practitioner (GP) for a symptom that cannot be explained immediately, but the symptoms improve within 2 weeks [6]. Moderate MUPS have an estimated prevalence of approximately 15%, where patients still experience unexplained symptoms after three months without a diagnosis of a functional somatic syndrome [6]. Patients with chronic MUPS will have a symptom duration of at least six months, with the presence of a functional somatic syndrome, such as fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome, or a somatic symptom disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [4,6,7]. Patients with chronic MUPS occur in approximately 2.5% in primary care, and 3% of the GP consultations are MUPS consultations [1,8].

Despite the low prevalence of chronic MUPS, the burden is substantial [1], with a high impact on patients' quality of life and daily functioning. Compared with the general population, as well with other patient groups such as major depressive disorder and cancer patients, patients with chronic MUPS report a lower quality of life [9,10]. Moreover, patients with MUPS consult a GP more frequently, but GPs find adequate management of MUPS challenging [11].

GPs frequently focus on exclusion of a somatic disease by recommending somatic interventions such as drug prescriptions, an investigation or a referral to a specialist; while patients often do not request for somatic interventions [12]. Furthermore, GPs face difficulty in the timely recognition of patients with MUPS [13]. On average, it takes two years to obtain a diagnosis. During this time period patients have on average 15 GP consultations, 8 visits to a hospital specialist and 14 sessions with the physical therapist [10]. Almost 40% of patients with MUPS report absenteeism from work [10]. As a result, MUPS are associated with increased direct and indirect costs related to health care expenditure as well as work and insurance related costs [10,14].

Much research has been conducted on effective interventions for chronic MUPS. Neurosciences-based therapeutic education, cognitive behavioral therapy, and exercise therapy have been shown to be effective treatment modalities in patients with MUPS [15-18]. Overall, the vast majority of these studies included patients with chronic MUPS. So far little research has been conducted in patients with moderate MUPS, partly due to the fact that adequate methods for early identification are lacking. Early identification of patients with moderate MUPS would enable interventions directed at prevention of chronicity, which ultimately might decrease the burden of these symptoms for patients, health care professionals and society.

Recently, a screening method (PRESUME; preventive screening of medically unexplained physical symptoms) has been developed to identify patients with moderate MUPS using data from the electronic medical record of the patient's GP as shown in Figure 1 [19]. The PRESUME screening method showed acceptable prognostic accuracy over a five-year follow-up [19]. For patients with moderate MUPS, we developed a proactive, blended, and integrated mental health and physical therapy care program to prevent chronicity. This is a 12-week program consisting of 4 face-to-face consultations with the mental health nurse and 5 physical therapy sessions, which are supplemented with a Web-based program (e-Exercise). Blended care has already proven to be effective in other studies [20,21] and it helps to promote self-management.

Figure 1. PRESUME screening method.
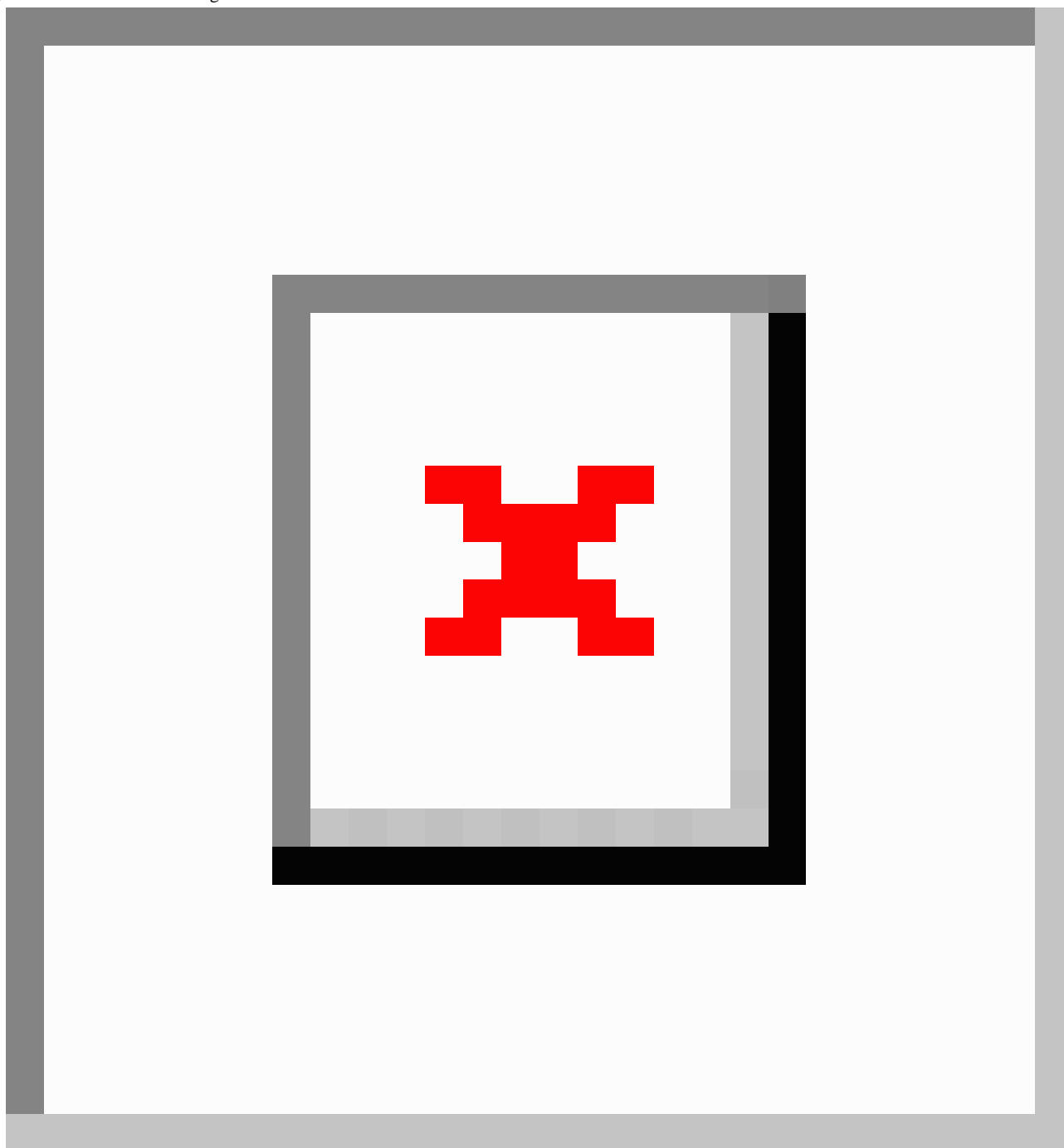
The primary objective of the present study is to investigate the effectiveness of the proactive, blended and integrated mental health and physical therapy care program (PARASOL) on impact of symptoms, as well as the physical and mental dimensions of quality of life in patients with moderate MUPS in comparison with usual care. Secondary objectives are to study the effect on severity of (psychosocial) symptoms, general health, physical behavior, illness perception, and self-efficacy in patients with moderate MUPS as well as to determine the cost-effectiveness of this program.

Methods

Study Design

A prospective, multicenter cluster randomized clinical trial will be conducted. The study has been approved by the Medical Ethical Committee of University Medical Center Utrecht, the Netherlands. The blended PARASOL intervention will be compared with usual care. An overview of the study procedure is shown in Figure 2.

Participants

Patient selection

Patients with moderate MUPS will be identified in the participating practices using 3 strategies. The first strategy is to use the PRESUME screening method. All patients in the routine care database of a GP are anonymously screened in a stepwise selection, based on a consultation frequency above five, with exclusion of chronic diseases (eg, chronic obstructive pulmonary disease, hypertension or diabetes mellitus) and psychiatric diagnoses (eg, schizophrenia, anxiety disorder or depressive disorder) and the presence of any of the 104 MUPS related International Classification of Primary Care codes. The prognostic accuracy of this PRESUME screening method for identification of moderate MUPS patients is moderate [19].

Figure 2. Overview of the study.
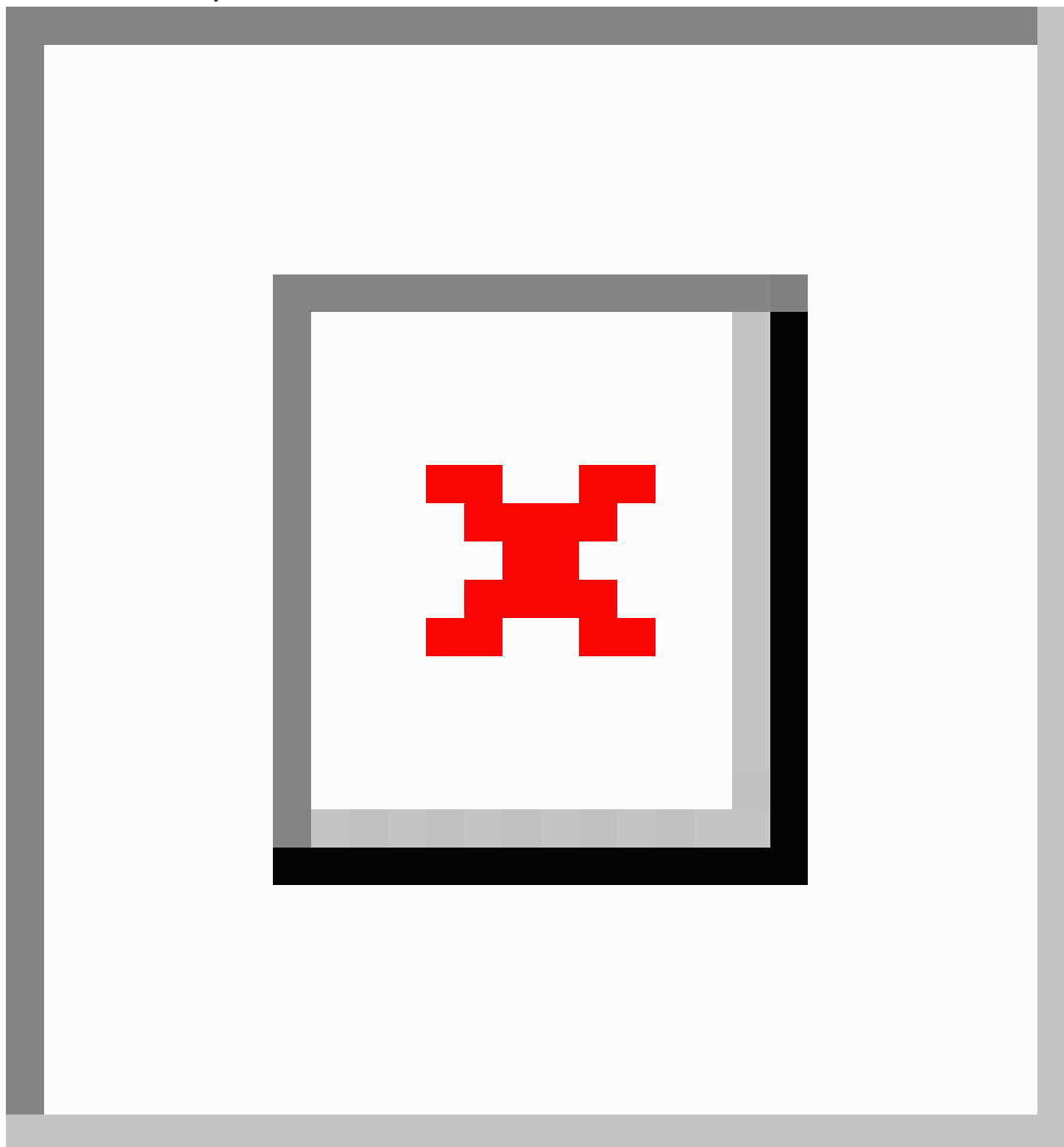
Since the PRESUME screening method is over inclusive and not meant to set an accurate diagnosis of MUPS in individual patients, all identified patients with moderate MUPS will be screened by their GP for eligibility [19]. As a consequence, the expected prevalence of patients with moderate MUPS is less than the 2.4% according to the PRESUME screening method

[19]. The GP will exclude patients based on the following criteria: (1) having another chronic somatic or psychiatric disease, (2) receiving a medically explained diagnosis between identification using the PRESUME screening method and the time of inclusion, (3) having complaints with a duration of less than 1 month, in which case further diagnostic evaluation of

the symptoms is needed, and (4) unable to participate as determined by the GP, due to a life-threatening condition, a shortened life expectancy, a major life event in the past month or a MUPS targeted multidisciplinary intervention in the past 12 months.

All remaining eligible patients will proactively be approached by their GP, by sending them an invitation letter with study information.

Secondly, GPs will recruit patients during consultations if they meet the following criteria: ≥18 years of age, ≥5 general practice consultations during the past twelve months, medically unexplained physical symptoms, and the diagnostic phase is completed. When a patient is eligible, the GP can give the contact details of the researchers of the PARASOL study to the patient.

The last strategy will be open recruitment in participating health care centers. Flyers with information about the PARASOL study will be provided in the waiting rooms and included in the newsletter of the health care centers. Patients who are willing to participate can contact the researcher by phone or by mail. Subsequently, the researcher will determine whether the patient is eligible by asking if the patient is older than 18 years, has had ≥5 general practice consultations during the past twelve months, and if the patient has medically unexplained physical symptoms.

All patients who are willing to participate in the PARASOL study, will have to have access to the internet and have mastered the Dutch language. When a patient is willing to participate, they can contact the researcher by phone or email. The researcher will answer any possible questions, give further information, and will make an appointment for the patient to sign informed consent and a baseline measurement evaluation. Additionally, patients in the intervention group will be invited to participate in the blended PARASOL intervention.

Study centers

The Leidsche Rijn Julius Health Care Centers (LRJG; 5 health care centers with 40,000 patients) and the Eindhoven Corporation of Primary Health Care Centers (SGE; 10 health care centers, 70,000 patients) will participate in the study. All relevant disciplines—general practitioners, physical therapists, and mental health nurses—are available and willing to participate.

Randomization Procedure

Cluster randomization will be performed at the level of the participating health care centers. Health care centers will randomly be assigned to either the intervention group or the control group (usual care) using a Web-based random generation of a sequence of numbers. Through cluster randomization, we will avoid professionals within one health care center offering both the blended PARASOL intervention and usual care, as this could cause potential contamination effects [22]. A higher drop-out rate in the intervention group is expected since psychological therapies have a 7% higher proportion of drop outs compared with usual care [18]. The blended PARASOL intervention combines both mental health and physical therapy

sessions. Therefore, an unequal randomization on cluster level will be conducted. Of the 15 included health care centers, 8 will be randomized to the blended PARASOL intervention and 7 will be randomized to the control group. After randomization of the health care centers, the selection and inclusion procedure of patients with moderate MUPS will be performed.

Intervention Program

The health care program is a proactive, blended, and integrated care program offered by a physical therapist and mental health nurse. The program will start with a physical approach since patients' perception of the symptoms usually has a somatic focus and MUPS patients are often reluctant to accept psychological oriented treatments [23,24]. The aim of the health care program is to reduce complaints of moderate MUPS, stimulate self-management, and prevent chronic MUPS. The health care program is focused on patients' insight, perception of symptoms, and modifiable prognostic risk factors for the development of chronic MUPS, using a cognitive behavioral approach and therapeutic neuroscience education as well as encouraging self-management and an active lifestyle using graded activity (details are provided in Multimedia Appendix 1). It consists of 3 steps and the face-to-face sessions will be integrated with eHealth modules, called blended health care. The content of the eHealth modules will be discussed during the face-to-face sessions. Details of the 3 steps are listed below:

1. Intake: The program will start with an intake session with both the physical therapist and the mental health nurse. During the intake session the complaints, treatment goals, treatment demand, and perpetuating factors of the patient will be identified according to the somatic, cognitive, emotional, behavioral, and social factors (SCEGS) model [3]. After the intake the physical therapist and mental health nurse discuss the complaints, treatment goals, and treatment demand.
   a. The physical therapist will focus on the somatic complaints (ie, physical symptoms, duration and course of symptoms, severity of symptoms, and physical functioning) and will conduct a physical examination to get insight to factors that are related to the content of the health care program (eg, posture and movement, breathing patterns, and muscle tension) and to determine if symptom specific exercises are needed.
   b. The mental health nurse will focus on cognitive, emotional, behavioral and social complaints.

2. Face-to-face sessions:
   a. Patients will have 4 face-to-face sessions with the physical therapist (week 1, week 3, week 6 and week 12) where the focus will be on the perception and acceptation of physical complaints of the patients. The physical therapist will start with education regarding the unexplained symptoms. Therapeutic neuroscience education according to the sensitization model is of particular interest due to patient's somatic fixation and anxiety for a severe disease [17]. Concurrently, graded activity will be used to gradually expand activities performed by the patient using principles of operant conditioning [25,26]. The graded activity schedule can

be performed in daily life. In week 6, the physical therapist will discuss the patients' lifestyle (eg, exercise, sleep, and relaxation) with the focus on behavioral changes to promote a healthy lifestyle. In week 12, the physical therapist will discuss long-term goals as well as how patients can maintain a physically active lifestyle.

b. Patients will have 3 face-to-face sessions with the mental health nurse (week 1, week 3, and week 6). In all 3 face-to-face sessions the mental health nurse will train coping strategies according to perpetuating factors and operant conditioning [25], with the focus on changing perception and acceptation. The mental health nurse will start with education regarding general perpetuating factors with the link to possible perpetuating factors of the patient. In the next 2 face-to-face sessions, the link between the perpetuating factors and patients coping strategies will be made, with the focus on behavioral change.

3. eHealth modules: The Web-based part of the health care program consists of exercises (instruction videos) and information modules on self-management and educative themes (description and videos). The modules consist of 3 components which are listed below.

a. Graded activity, an activity-focused method with operant conditioning behavioral principles with 3 consecutive phases. In the starting phase, the patient will choose an activity they want to expand gradually. The patient will perform the chosen activity to their tolerance level (ie, until pain or fatigue drives them to stop; this will be pain-contingent) while their performance is recorded in distance units, time, or number of repetitions. After at least 3 pain-contingent measurements, occurring over several days, a baseline will be determined, and the patient sets his or her individual treatment goal. In the treatment phase, the chosen activity will be increased gradually (ie, time-contingent) and an individual scheme will be drawn up. In the integration phase, patients will be stimulated to adhere to the activity in their daily living [25,26]

b. Videos of prescribed home exercises by their physical therapist

c. Videos and information on self-management and educational themes such as central sensitization, perpetuating factors, graded activity, behavioral change, stress, coping, relaxation, lifestyle advice, creating and performing an exercise plan, and avoiding a relapse.

Usual Care

Patients in the control health care centers will get care as per usual without any restrictions. This care could include care of the GP, physical therapist, mental health nurse, and psychologist.

Outcomes

Primary Outcome

The primary outcome measures are impact of symptoms and quality of life.

Secondary Outcomes

Several secondary parameters will be measured to determine the influence of the blended e-Exercise health care program on severity of physical and psychosocial symptoms, general health, physical behavior, illness perceptions, self-efficacy, and cost-effectiveness.

Measurements

Three time points (baseline, 3-month, and 12-month follow-up) will be used for data collection. In addition, cost questionnaires will also be sent to the patients at 6 and 9 months. Furthermore, the impact of symptoms will be measured weekly between 0 and 3 months, followed by monthly measurements between 6 and 12 months. We offer no financial incentives to complete questionnaires or to carry the Acitv8 activity monitor. The measures that will be collected are listed below and Table 1 gives a summary of all measures that will be collected.

- Impact of symptoms, which addresses adequate relief using a validated single question, which is scored on a dichotomous scale ("Over the past week have you had adequate relief of your symptoms?") [27,28]. A responder for adequate short-term relief is defined as a patient who will report adequate relief of their symptoms for at least six of the twelve weeks between the baseline and three-month follow-up. In addition, a responder for adequate long-term relief will report adequate relief of their symptoms for at least three of the six months between the 6- and 12-month follow-up. Otherwise, a patient will be defined as a nonresponder. Adequate relief is a validated clinically relevant endpoint and is defined at the point where the individual patient is satisfied with treatment [29].

- Quality of life will be measured with the 36-Item Short Form Health Survey (RAND-36) health survey. The RAND-36 is a valid and reliable self-reported questionnaire [30]. The questionnaire consists of eight subscales, namely physical functioning, social functioning, role-physical or emotional problems, mental health, vitality, bodily pain, and general health. A higher score on the scale of 0-100 indicates a better quality of life [30,31].

- Severity of symptoms, defined as self-perceived pain and fatigue in the past week, will be measured with an 11-point numeric scale (score 0-10) [32].

- Severity of psychosocial symptoms will be measured with the Four-Dimensional Symptom Questionnaire (4DSQ) questionnaire. This questionnaire consists of 4 subscales, namely distress, depression, anxiety, and somatization [33,34].

- Self-perceived health will be measured with the EuroQol-5D (EQ5D) questionnaire. This questionnaire will measure the perceived health on five levels (ie, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) [35].

- Physical movement behavior will be measured with the Activ8 activity monitor [36]. The Activ8 is a validated activity monitor to measure physical behavior by measuring several activities and postures (lying, sitting, standing, walking, running, and cycling). Patients will wear the Activ8 activity monitor for 1 week at varying intervals

during the study. They will wear it at baseline, at 3 months follow-up, and at 12 months follow-up.

- Illness perceptions will be measured using the Brief Illness Perception Questionnaire. This questionnaire is an eight-item scale designed to assess cognitive and emotional representations of illness on an ordinal scale (0-10) [37,38].

- Self-efficacy will be measured with the Hei-Q questionnaire, which is a user friendly, valid, and reliable questionnaire specifically developed to evaluate patients' education and self-management programs for patients with chronic complaints [39].

- Health care use and indirect costs through illness and absenteeism will be measured with Trimbos/iMTA Questionnaire for Costs associated with Psychiatric Illness (TIC-P) questionnaire to evaluate the cost-effectiveness of the program in terms of costs per Quality Adjusted Life Years (QALYs) [40]. Patients will be asked to complete the cost questionnaire every 3 months, since this questionnaire focuses on health-related costs in the past 3 months. QALYs will be measured using the EQ-5D scores [41]. In this way, we will get information of patients' healthcare utilization and (unpaid) productivity losses.

- Besides the above parameters, the efficacy, barriers, and facilitators of the Web-based component of the blended PARASOL intervention from a patient's perspective will be measured using the System Usability Scale (SUS). The SUS will be completed by patients of the intervention group at the end of the health care program (3-month follow-up).

The questionnaire will measure the perceived usability by ten statements which can be scored on a 5-point Likert scale ('totally agree' to 'totally disagree'). The SUS is a simple, valid, and reliable measurement and is often used the evaluate the usability of eHealth applications [42].

Other Measures

Demographic and clinical variables such as age, gender, education level, work situation, duration of complaints, and possible comorbidities will be measured at baseline. Possible comorbidities will be measured again at 3 and 12 months after baseline to determine if patients have developed comorbidities or any chronic MUPS syndromes such as fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome.

Sample Size

The number of eligible patients was calculated according to Campbell et al for cluster randomized trials [43]. The power calculation is based on an intracluster correlation coefficient of 0.04 [44,45] and a minimum of 20 patients per health care center. Additionally, we assume a minimal clinical detectable change of >10 points in the sum score of physical functioning of the RAND-36 questionnaire, and a SD of 23.8 [10]. Based on these assumptions and a power of 80% (alpha=.05), at least ten health care centers and 206 participating patients are needed. With an expected drop-out rate of 20%, a total of 248 participating patients (124 patients per arm) are needed for the study.

Table 1. Summary of measures to be collected.

Outcome measures	Data collection instrument	Follow-up measurements				
		Baseline	3 months	6 months	9 months	12 months
Primary outcome measures						
Impact of symptoms[a]	Adequate Relief question	✓	✓			✓
Quality of life	36-Item Short Form Health Survey (RAND-36)	✓	✓			✓
Secondary outcome measures						
Pain	Numeric Rating Scale	✓	✓			✓
Fatigue	Numeric Rating Scale	✓	✓			✓
Severity of psychosocial symptoms	Four-Dimensional Symptom Questionnaire	✓	✓			✓
General health	EuroQol-5 Dimensions	✓	✓			✓
Physical behaviour	Activ8 activity monitor	✓	✓			✓
Illness perceptions	Brief Illness Perception Questionnaire	✓	✓			✓
Self-efficacy	Health Education Impact Questionnaire	✓	✓			✓
Cost-effectiveness	Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness	✓	✓	✓	✓	✓
Barriers and facilitators of the blended e-Exercise health care program	System Usability Scale		✓			
Other measures						
Age	Questionnaire	✓				
Gender	Questionnaire	✓				
Education level	Questionnaire	✓				
Work situation	Questionnaire	✓				
Duration of complaints	Questionnaire	✓				
Possible comorbidities	Questionnaire	✓	✓			✓

[a]Measured weekly between baseline and 3 months follow-up, and monthly between 6 and 12 months follow-up.

Statistical Analysis

Statistical analysis will be performed using IBM SPSS 22. Statistical analysis will be performed according to the intention-to-treat principle. Any missing values will be imputed with the Multivariate Imputation by Chained Equations. Descriptive statistics will be used to describe the number of patients with moderate MUPS (as identified using the PRESUME screening method) which are excluded by their GPs, how many patients are recruited with the 3 different strategies, as well as how many patients do not complete the blended PARASOL intervention. Additionally, descriptive statistics (frequencies, t-test and chi-square test) will be used to describe the demographic characteristics of the study population and to explore baseline comparability. Differences in effectiveness of the blended PARASOL intervention will be analyzed using longitudinal mixed methods analyses. In this way, we can correct for independence of observations within patients as well as take into account possible variations between clusters and health care professionals. Analyses will be corrected for potential confounders (eg, age, gender, and psychiatric comorbidity) and potential interactions terms (eg, age in the use of the Web-based component of the PARASOL intervention) will be checked.

Furthermore, the cost-effectiveness of the blended PARASOL intervention will be clarified with an incremental cost-effectiveness ratio based on the costs per QALY. All costs measured by the TIC-P (health care use and indirect costs of illness and absenteeism) are used to calculate the incremental cost-effectiveness ratio.

Results

The components of this intervention are based on results of a literature search and focus groups with experts (general practitioners, physical therapists, mental health nurses, and psychologists) [46]. The content of the information, self-management, and exercise modules were specifically developed for the current study. The functionality of the online program used in this study is based on the blended exercise intervention for patients with hip or knee osteoarthritis (e-Exercise) [47].

Before the start of the intervention program, physical therapists and mental health nurses of the experimental health care centers received two days of training on the content of the blended PARASOL intervention. The training consisted of presentations

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on the study population, central sensitization, therapeutic neuroscience education, graded activity, and perpetuating factors for all professionals involved in the study. Furthermore, the training included discussion of the content of the online modules and instructions on their implementation. During the study, a follow-up training session for the therapists will be conducted to ensure adherence to the treatment protocol.

The recruitment of health care centers started in June 2016 and inclusion of patients began in March 2017. Follow-up assessments of patients are expected to be completed in March 2019.

Discussion

In this randomized clinical trial, the effectiveness (including cost-effectiveness) of the PARASOL intervention, a proactive blended and integrated mental health and physical therapy intervention program, will be studied.

Although the study is well-planned and involves all relevant stakeholders, the conduction of the study will present several operational challenges. The first challenge has been identified as GPs motivation to actively participate in the recruitment of patients with moderate MUPS. Patients with MUPS are a difficult patient group for GPs and often the patient-doctor relationship is under pressure due to mismatches between the expectations of the patient and doctor [48]. To motivate GPs to recruit patients with moderate MUPS, information about the PARASOL study will be sent to them beforehand. During the study, GPs will be individually informed if one of their patients is participating in the PARASOL study. Furthermore, all participating GPs will be sent updates at 3-month intervals informing them about total patient inclusion in the study, as well as patient inclusion per GP.

A second challenge identified is the recruitment of adequate patient numbers to achieve the desired statistical power. Patients with moderate MUPS will be identified using the PRESUME screening method, following which they will be proactively approached by their GP. This proactive approach may lead to patients in a non-symptomatic phase or without a treatment demand being contacted. Consequently, these patients might be less motivated to follow the blended PARASOL intervention aiming to prevent chronicity of MUPS. To deal with this challenge, setting individual treatment goals has been identified as an important part of the intake session. It should be noted that the face-to-face sessions are not performed on a weekly basis to not only reduce the burden for patients, but more importantly to encourage self-management.

A third challenge is the potential drop-out rate in the control group since these patients will not be receiving the blended PARASOL intervention and therefore may be less motivated to participate in the study. To deal with this challenge, patients in the control group will be offered to follow the blended PARASOL intervention after the study ends.

A final identified challenge is the non-usage of the Web-based component of the blended PARASOL intervention. Previous studies have shown that patients in online interventions are less motivated and feel less pressure to continue with the intervention compared to face-to-face interventions [49]. To combat this, patients will receive email reminders for the eHealth modules weekly. Furthermore, the PARASOL intervention has been designed as a blended care program, and this is therefore expected to maximize adherence compared to self-guided internet interventions [50].

Besides these challenges, there are several strengths and limitations in the design of the study that should be noted. The first strength of this study is that physical therapists and mental health nurses will participate in two days of intensive training about the content of the blended PARASOL intervention. This will minimize the differences in the care offered by professionals at different health care centers during the health care program [51]. In addition, a meeting with the participating physical therapists and mental health nurses will be organized after 6 months to discuss the content of the blended PARASOL intervention as well as any possible difficulties faced. The 12-month follow-up measurement is another strength of this study as it will result in data being obtained about long-term effectiveness (and cost-effectiveness) of the program. The PARASOL intervention stimulates self-management by focusing on achieving a healthier lifestyle as well as the adoption and maintenance of exercise behavior. Since the process of adopting a change to maintaining a change takes at least six months, a long-term follow-up is of particular interest [52]. A third strength of this study is performing cluster randomization at the level of the health care centers as this ensures that a contamination-effect will be avoided [22]. Finally, this is the first study, to the best of our knowledge, that investigates the effectiveness of an intervention program for patients with moderate MUPS to prevent chronicity.

The first identified limitation of this study, is that it is unblinded. Patients, health care professionals, and the researchers are aware all of the group allocated to the blended PARASOL intervention. This may lead to bias mechanisms such as response bias or observer bias being present in the data [53]. One of the aims of the training provided to the healthcare professionals involved in the study is to avoid response bias from the health care professionals. Observer bias will be avoided by using a measurement protocol, well trained observers, and standardized outcome measures. A second limitation is that overtreatment may occur since not all patients with moderate MUPS will be prevented from developing chronic MUPS after completing the PARASOL intervention. This could lead to higher health care costs if patients are still consulting health care professionals after completing the PARASOL intervention. However, an early intervention for patients with moderate MUPS may lead to a decrease of direct and indirect costs on long term if chronic MUPS is prevented. Therefore, one of the secondary objectives is to determine the cost-effectiveness of the PARASOL intervention. A third limitation is complexity of the design of the study due to the use of cluster randomization. Cluster randomized trials are more complex, require more patients to obtain equivalent statistical power, and require more complex analysis [43]. However, in the sample size calculation and statistical analysis, this possible design effect has been taken into account.

This study is the first trial that investigates the effectiveness (including cost-effectiveness) of a blended care program in patients with moderate MUPS. Therefore, this study will provide relevant results regarding short- and long-term effectiveness of a multidisciplinary, blended care program to prevent chronic MUPS.

Acknowledgments

Conflicts of Interest

None declared.

Multimedia Appendix 1

Schematic view of the blended health care program.

[PDF File (Adobe PDF File), 27KB - resprot_v7i5e120_app1.pdf]

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Abbreviations

4DSQ: Four-Dimensional Symptom Questionnaire
EQ5D: EuroQol-5D
GP: general practitioner
ICPC: International Classification of Primary Care
MUPS: medically unexplained physical symptoms
PRESUME: preventive screening of medically unexplained physical symptoms
RAND-36: 36-Item Short Form Health Survey
TIC-P: Trimbos/iMTA Questionnaire for Costs associated with Psychiatric Illness
QALY: Quality Adjusted Life Years

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<u>Protocol</u>

Engagement Strategies for Self-Monitoring Symptoms of Bipolar Disorder With Mobile and Wearable Technology: Protocol for a Randomized Controlled Trial

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Abstract

Background: Monitoring signs and symptoms in bipolar disorder (BP) is typically based on regular assessments from patient-clinician interactions. Mobile and wearable technology promises to make monitoring symptoms in BP easier, but little is known about how best to engage individuals with BP in monitoring symptoms.

Objective: The objective of this study was to provide the rationale and protocol for a randomized controlled trial that investigates engagement strategies for monitoring symptoms of BP, including the strategies of using activity trackers compared with self-reports and reviewing recorded symptoms weekly with an interviewer.

Methods: A total of 50 individuals with BP will be recruited from the Prechter Longitudinal Study of Bipolar Disorder at the University of Michigan to participate in a 6-week study. Participants will monitor their symptoms through an activity tracker (Fitbit Alta HR) and a mobile phone app designed for this study. In addition to monitoring symptoms, participants have a 50-50 chance of being assigned to an arm that reviews self-reports and activity information weekly. Statistical tests will be performed to test hypotheses that participants adhere to activity tracking significantly more than self-reporting, prefer activity tracking significantly more than self-reporting, and better adhere to both activity tracking and self-reporting when reviewing collected information weekly.

Results: Recruitment commenced in November 2017. The first group of participants began the study in January 2018.

Conclusions: This study aims to establish strategies to engage individuals with BP in monitoring their symptoms with mobile and wearable technology. Better engagement strategies are expected to aid current efforts in bipolar research and clinical care, from the development of new mobile phone apps to providing the right intervention to the right individual at the right moment.

Trial Registration: ClinicalTrials.gov NCT03358238; https://clinicaltrials.gov/ct2/show/NCT03358238 (Archived by WebCite at http://www.webcitation.org/6yebuNfz5)

Registered Report Identifier: RR1-10.2196/9899

KEYWORDS

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Introduction

Background

Bipolar disorder (BP) is a chronic illness of pathological shifts in mood ranging from mania to depression. Management of BP is typically a combination of medication with psychosocial therapy; however, relapse is common, resulting in overall inadequate care in practice and over the course of the illness [1]. With limitations in treatment options, along with imprecise guidelines on when, where, and how to intervene, promising psychosocial therapies require adaptive strategies to better address the specific needs of individuals in a timely manner [2]. To accomplish this requires evidence-based practices for adapting a psychosocial therapy, for which mobile health and wearable technology play a key role [3].

Effective adaptive interventions hinge on collecting momentary and pertinent observations. For BP, observations would ideally be collected as frequent as twice daily and for as long as weeks or years to capture the following characteristic features of BP: diurnal patterns [4], rapid mood shifts [5], full-length manic and depressive episodes [6], and waiting periods before medications take effect [7]. Monitoring symptoms in BP is also important, irrespective of the need for adaptive interventions. The World Health Organization (WHO) recommends that individuals with BP monitor their symptoms, and psychosocial therapies for BP often require individuals to monitor their symptoms [8].

Historically, symptoms in BP are monitored through self-reporting, often with mood on a one-dimensional scale such as the Mood 24/7 scale [9] and the National Institute of Mental Health (NIMH) Life Chart Method [10]. Mood, however, may not be one-dimensional, as manic and depressive symptoms frequently appear together [11]. NIMH's Research Domain Criteria [12], for example, considers a negative valence domain separately from a positive valence domain, allowing for the possibility that each valence domain is regulated separately. Self-reports also depend on an individual's mood and time of day [4] and require individuals to actively record symptoms, a burden that leads to disengagement [13,14]. In sum, self-reports are subjective and time-intensive and lose information, which may limit their utility in charting BP.

Increasingly, BP symptoms are being monitored *passively* through sensors on mobile phones and wearable devices [15-21]. Mobile phone platforms MONitoring, treAtment and pRediCtion of bipolAr Disorder Episodes (MONARCA) [22] and Predicting Individual Outcomes for Rapid Intervention (PRIORI) [23] predict mood from patterns of speech and behavior from recorded calls, number of phone calls, and phone call duration. Wearable devices such as activity trackers monitor physical activity, as well as circadian and sleep rhythms. Circadian and sleep rhythms are regulated in therapies such as sleep deprivation and interpersonal and social rhythm therapy [24,25]. Circadian rhythms are thought to be central to BP etiology, with connections to risk genes, animal models, and pharmacological therapy [26], and actigraphic variables are linked to genetic differences between individuals with BP-I and without BP-I that include later wake times, longer sleep durations, and lower

activity levels in BP-I subjects during euthymia [27]. Data from mobile phone and wearable devices can also be fitted to models of circadian and sleep rhythms [28], which have provided insight into normal sleep habits around the world [29].

Objectives

The benefits and needs are clear for monitoring symptoms of BP using mobile and wearable technology, but we still do not know how best to engage individuals with BP in this task. In this paper, we describe the protocol for a study to answer this question (ClinicalTrials.gov NCT03358238). Briefly, individuals with BP will interact with a mobile phone app and activity tracker over 6 weeks. They will report their symptoms twice-daily with the mobile phone app while activity, sleep, and heart rate are recorded with an activity tracker. The study implements 3 engagement strategies: using activity trackers rather than self-reports; reviewing recorded symptoms with another person on a weekly basis; and synthesizing a person's data into charts and graphs. We hypothesize that individuals with BP will prefer and better adhere to monitoring their symptoms when using activity trackers over self-reports and when reviewing their recorded symptoms weekly with an interviewer.

Methods

Recruitment

In total, 50 individuals with BP will be recruited from the Prechter Longitudinal Study of Bipolar Disorder [30] to participate in a 6-week, 2-arm randomized controlled trial. This 6-week study has been approved by institutional review boards at the University of Michigan (HUM126732) and University of Wisconsin (2017-1322). Participants in the Prechter study have already completed a Diagnostic Interview for Genetic Studies about their health and mental illness history. We will access the diagnostic information and other data from the longitudinal study so as not to repeat the interview process. Individuals will be included if they (1) have agreed to be contacted for future research, (2) have a mobile phone, and (3) have a diagnosis of BP. Participation is open to men and women; to adults (aged 18 years or older); and to all ethnic and racial groups. To select participants from the larger trial, a data manager pulled a query of participants with diagnoses of either BP I, BP II, or BP NOS (not otherwise specified) and who have authorized contact for future studies. Participants are ordered by authorization date, with most recent dates at the top of the list and recruitment emails are sent in this order. Individuals who express interest and have a mobile phone are then consented.

The study aims to be balanced by age and gender and to achieve adequate representation of minorities as reflected by the diversity of Washtenaw and surrounding Counties of Michigan, in which most participants live. All participants will be consented, which involves a discussion over the phone, followed by submission of consent electronically through the data capture software REDCap (see Multimedia Appendix 1 for Informed Consent document). Sample size and observation length are based on 3 auxiliary studies of the Prechter study finding significant associations between variables and significant

differences in measurements between two groups, assuming about 10% to 20% attrition.

Randomization

Each participant is randomly assigned to one of the two arms (Arm NR=No Review or Arm R=Review), stratified by age and gender. Each participant has a 50-50 chance of being assigned to Arm R. Following weekly mood assessments, Arm R reviews information collected over the week with an interviewer, whereas Arm NR does not discuss this information. Subjects and interviewers will necessarily be unblinded. A randomized list of assignments to one of the two arms was generated for 4 groups: women <40 years of age (N=13), women ≥40 years of age (N=13), men <40 years of age (N=12), and men ≥40 years of age (N=12). The randomized list was generated using a random number generator in Matlab (Mathworks; Natick, MA) and a block design, which involves generating random assignments in smaller blocks of participants and then randomly permuting the order of blocks. Because the 2 women groups had an odd number, these blocks were each unbalanced but together ensured equal participants in each arm; the arm that was over-represented in each group was chosen uniformly at random. Additional randomized blocks were appended to the randomization list in case of dropout. Although unblinded, arm assignments are not revealed until individuals are recruited and consented to avoid selection bias.

Study Design

A summary of participation in the study is given in Table 1. Participation involves 7 weekly phone interviews and the use of mobile and wearable technology over 6 weeks. Each participant wears a Fitbit Alta HR to collect information about physical activity, sleep, and heart rate. They also download a mobile phone app designed specifically for this study called Lorevimo, which we will discuss in detail below. Briefly, the study app Lorevimo prompts the user twice-a-day (once in the morning and once in the evening) on questions about manic and depressive symptoms and medication adherence. The mobile phone app also allows the participant to review and chart information collected from self-reported app survey and activity tracker and from data processed with computational algorithms. Participants are compensated for each phone interview but not using the app or activity tracker (see Multimedia Appendix 2 for detailed protocol).

The first phone interview marks the start of the study for each participant. The interviewer conducts 3 surveys over the phone to assess mood and general health. Manic symptoms are assessed with a Young Mania Rating Scale (YMRS) [31]; depressive symptoms are assessed with a Structured Interview Guide for the Hamilton Rating Scale of Depression (SIGHD) [32]; and general health is assessed using the 36-Item Short Form Health Survey (SF-36) developed by RAND [33]. After the first phone interview, participants are contacted by phone at weekly interviews. The next 5 interviews will also entail an assessment of manic and depressive symptoms using the YMRS and SIGHD. In addition to these assessments, participants in Arm R will also review with the study team what they reported over the week about mood and medication adherence, and what the activity tracker reported about their sleep, heart rate, and physical activity. The seventh and final phone interview marks the end of the 6-week study. At this interview, the interviewer again conducts 3 surveys used at the start of the study: YMRS, SIGHD, and SF-36. In addition, the interviewer also conducts a final survey designed specifically for the study called the Engagement Assessment (available in the Multimedia Appendix 3).

Design of Study App

We designed an app, called Lorevimo, for monitoring symptoms in BP. Its name derives from the 3 main functions of the app: Log, Review, and Visualize your Mood (Figure 1). We focused on developing a *simple* app with minimal components, so results from this study could generalize to other tracking apps in BP (which are numerous) [34]. At a minimum, we wanted the app to allow users to log their symptoms and receive reminders to log their symptoms. We then added 2 functionalities—reviewing, and visualizing their logged symptoms—to encourage app usage, which we discuss in detail below.

Lorevimo is currently restricted to participants by requiring a coded username and password provided to each participant upon entering the study. Participants can find the free app for Android through Google Play and for iPhone through iTunes. If participants are away from their phone, they can also access the app through any standard Web browser. However, push notifications are not available for the Web-based app. The app was developed using the online software Appery.io (Appery LLC; Walnut Creek, CA), which combines drag-and-drop functionality with Javascript to flexibly allow for quick development and advance control of development. Appery.io also provides each app with backend servers, database management, application programming interface integration, push notifications, and automatic packaging for each app into Android, iPhone, and Web-based apps.

Log Your Mood

Lorevimo's main function is to log manic and depressive symptoms and medication adherence (Figure 1). Users can log symptoms, once in the morning and once in the evening, to capture diurnal patterns in mood characteristic of BP. Morning and evening is defined based on a participant's self-reported wake and bed times on weekdays and weekends: respectively, the 6-hour window spanning 2 hours before to 4 hours after their typical wake time and the 6-hour window spanning 4 hours before to 2 hours after their typical bed time. Typical bedtimes or wake times are entered by the user when they first log into the app and can be changed anytime under Settings in the app. Automatic reminders via push notifications are sent at 2-hour intervals for individuals who are yet to log symptoms, are within the appropriate window, and not too close to their typical bedtime or wake time.

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Table 1. Summary of study participation and information collected on each participant.

Interaction	Instruments	Study days
Entrance phone interview	YMRS[a], SIGHD[b], RAND SF-36[c]	0
App self-report	3 items from YMRS, 3 items from SIGHD, medication adherence (only in the morning)	0-42, twice
Offline computed variables	Computed variables: circadian phase and amplitude and cumulative sleep debt	0-42
Activity tracker	Activity, sleep, heart rate	0-42
Weekly phone interview	Both arms: YMRS, SIGHD. Arm R only: review of collected data from app and activity tracker	7, 14, 21, 28, 35
Exit phone interview	YMRS, SIGHD, RAND SF-36, Engagement survey	42

[a]YMRS: Young Mania Rating Scale.

[b]SIGHD: Structured Interview Guide for the Hamilton Rating Scale of Depression.

[c]SF-36: 36-Item Short Form Health Survey.

Figure 1. Screenshots of study app Lorevimo, which derives its name from the app's 3 main functions: to log, review, and visualize your mood.
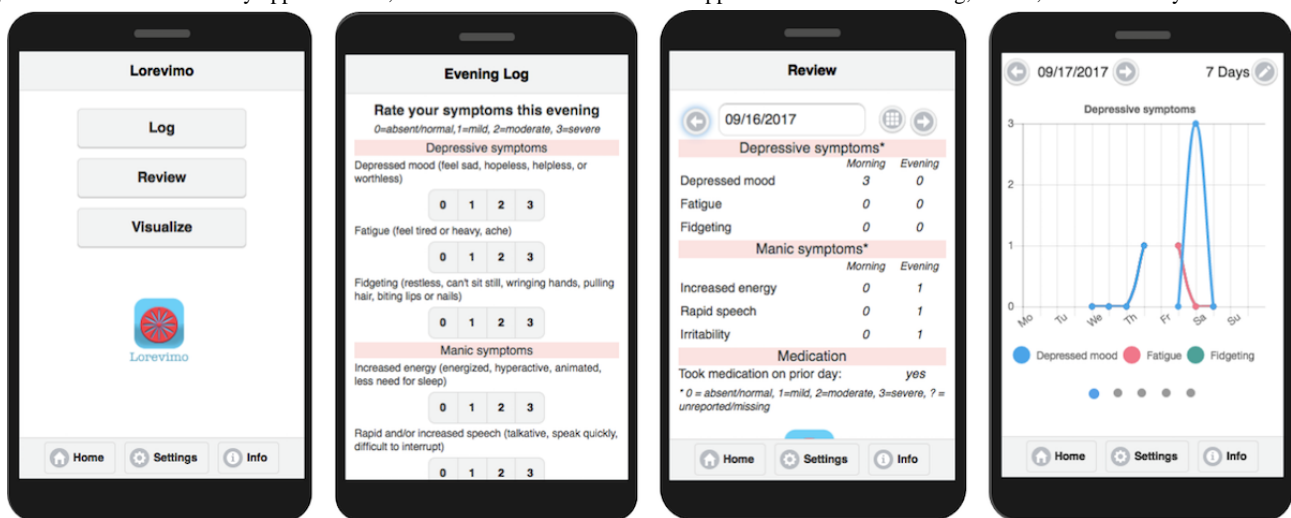
Six symptoms are logged each morning and evening: 3 for mania (increased energy, rapid speech, irritability) and 3 for depression (depressed mood, fidgeting, fatigue). In the morning, users also mark whether they took their medicine on the previous day. We remark that the 6 symptoms capture the various ways in which symptoms manifest in BP, including *anxious* depression (depressed mood+fidgeting); *anhedonic* depression (depressed mood+fatigue); *euphoric* mania (increased energy+rapid speech); *irritable* mania (irritability); and *mixed* states (depressed mood+increased energy). All symptoms are scored on a 0 to 3 scale with 0=absent/normal, 1=mild, 2=moderate, and 3=severe. Ordinal scales were used as opposed to visual analog scales to be consistent with YMRS and SIGHD to clearly identify the absence of symptoms as zero and to ensure individuals can discriminate between choices.

In choosing these 6 symptoms, our goal was to maximize the consistency between the logged symptoms via the app and our *gold standard* or *ground truth* for manic and depressive severity, without overburdening the user with long surveys. Our ground truth was total scores on the interview-based YMRS and SIGHD. We thus focused on logging 6 symptoms chosen from the YMRS and SIGHD. These 6 symptoms were identified from a preliminary analysis of longitudinal surveys of YMRS and SIGHD from 27 individuals with either BP I or BP II from the Prechter Longitudinal Study of Bipolar Disorder at the University of Michigan. Surveys were performed weekly, for a total number of weeks per individual ranging from 2 to 52 weeks, with a median of 20 weeks. Using this data, we performed an exhaustive search of all 6-item sets chosen from the 11-item YMRS and 17-item SIGHD. For each 6-item set, we built linear models, one to predict total YMRS score and one to predict total SIGHD score, from the corresponding responses for the 6 items and measured mean-squared error in each linear model. Samples were weighted inversely by the number of samples per person, to ensure individuals contributed equally to estimation. We then identified which 6-item set (of over 300,000 possible sets) had the smallest sum of mean-squared error for predicting YRMS scores and SIGHD score, which resulted in the aforementioned 6 symptoms. The resulting 6-item set has not been validated yet for use in a mobile app.

Review and Visualize Your Mood

The remaining 2 functions of the app are to provide users a place to *review* their reported symptoms and *visualize* their symptoms and Fitbit data with charts and graphs (Figures 1 and 2). Upon clicking Review from the app's home page, the user is shown a report on what they reported for the current day through the app, which consists of at most 6 morning symptoms, 6 evening symptoms, and whether they took their medication on the prior day. Missing items are left blank. The user can then

navigate to view reports from other days. Upon clicking Visualize from the app's home page, the user is shown a graph of their depressive symptoms over the past week. They can change the time period's length (3, 7, or 28 days) and ending day. Upon swiping left, they can also view manic symptoms, sleep patterns, activity and heart rate patterns, and daily circadian and sleep rhythms.

These functions were designed to serve dual roles: (1) to help an individual with BP manage their disorder and (2) to encourage individuals to continue to log their symptoms with the app. These roles may be accomplished in several ways. First, a participant who reviews/visualizes their symptoms should have increased awareness of symptoms, a cornerstone of many effective psychosocial therapies [2]. Second, the participant could gain insight into their illness, for example, helping them to recognize that when they exercise, their mood improves. Third, they could be warned about an impending manic or depressive episode, as they see their symptoms begin to reach severe levels. Meanwhile, if these functions indeed help a user manage their disorder, then they may be more greatly motivated to log their symptoms, which is ultimately the purpose of this study. Even if these functions do not help with BP management, individuals may still be motivated to log their symptoms and use their activity tracker, knowing that they will gain *information* from this transaction. Information-seeking is believed to be a mechanism by which individuals engage with mobile and wearable devices.

Activity Tracking

We give each participant a Fitbit Alta HR to track activity, sleep, and heart rate for the duration of the study. They are provided the original instructions that accompany the Fitbit for setting up the device. We do not provide additional instructions for setting up the Fitbit but do instruct them on how to provide us access to their Fitbit data and ask them to wear the Fitbit except to shower or charge the device. While mobile phones are capable of tracking activity and would be less intrusive as a wearable device thereby helping to reduce stigma, we opted for a wearable device to be able to track sleep and heart rate in addition to activity and to avoid differences in how activity is measured resulting from different mobile phone devices or different habits in how mobile phone devices are carried. Sleep and exercise may be important to track, as they are considered part of a healthy lifestyle and believed to be just as important in BP [8]. Furthermore, many clinical assessments of BP use measures related to sleep and activity, such as insomnia, psychomotor retardation, and energy levels [31,32]. Mania, for example, is marked by less need for sleep and increased activity, whereas depression is marked by decreased activity and hypersomnia. Heart rate may also be important to track in BP, since heart rate properties may reflect increased stress [35], a trigger of manic and depressive symptoms [36]. In sum, daily activity, sleep, and heart rate could be important markers of mood and targets for therapy.

Participants are asked to set-up their own Fitbit account and sync a Fitbit Alta HR to their own account. We then ask each participant to provide us access to their Fitbit data on activity, sleep, and heart rate. We store the access and refresh tokens granted to us and link these tokens to the participant's coded study username on a server. This server than queries Fitbit server once a day to collect daily information from participant's Fitbit. Collected activity information consists of steps, minutes active, minutes sedentary, distance traveled, calories when active, and total calories. Collected sleep information consists of sleep periods with duration; efficiency; start and end times; time in bed; levels; and minutes asleep, awake, to fall asleep, and after wake time. Finally, collected heart rate information consists of resting heart rate; and minimum heart rate, maximum heart rate, and duration in 4 different heart rate zones. Much of this information is relayed to the study app Lorevimo for participants to visualize over time.

Mathematical Modeling of Sleep and Circadian Patterns

Circadian rhythms are potentially important markers of BP but are not tracked by Fitbit. To that end, we model circadian rhythms using the Forger-Jewett-Kronauer model [28]. Light levels are usually inputted into the model to reflect its ability to shift circadian phase but since light is not measured by a Fitbit, we assume an individual is exposed to 150 lux when awake and 0 lux when asleep [29,37], whereas this latter information is available from the Fitbit. A homeostat component, another factor in sleep drive, will also be modeled such that it increases while awake and decays while asleep [38]. These models yield 4 markers: circadian phase, circadian amplitude, maximum homeostat, and minimum homeostat. These models are processed by a server with information relayed to the study app Lorevimo. A participant can view their circadian phase and maximum homeostat, which are respectively renamed *circadian midnight* and *sleep debt* for the app, through charts and graphs under the Visualize feature of the app.

Engagement Survey

We designed an *engagement survey* which will be administered over the phone at the end of the study (Multimedia Appendix 3). This survey consists of 17-items, each aimed at understanding how best to engage individuals with BP in monitoring symptoms with a mobile phone app and activity tracker. The engagement survey asks questions about their preference toward using a mobile phone app versus activity tracker, general feelings and attitudes toward using a mobile phone app, activity tracker, and charts/graphs for monitoring symptoms and toward reviewing information weekly with another person. Additional items ask participants to identify top 3 symptoms or patterns to monitor, top 3 barriers to monitoring symptoms, and top 3 uses for monitoring symptoms.

Figure 2. Screenshots of Visualize portion of study app showing data collected from Fitbit and variables computed from mathematical modeling. HR: heart rate.

Data Analysis

Primary Outcome Measures

We identified four primary outcome measures for evaluating how best to engage BP individuals in monitoring their symptoms with mobile and wearable technology. Specifically, our primary outcome measures test two engagement strategies for monitoring symptoms in BP: using activity trackers over mobile phone and reviewing data collected weekly with an interviewer. The former strategy is evaluated with the first and second primary outcomes: *proportion of participants who report they are more likely to use a* mobile phone *app over an activity tracker to monitor their symptoms* and *proportion of participants who have higher adherence rates for self-reporting symptoms than adherence rates for activity tracking.* Likelihood of using an app over an activity tracker is measured using the engagement survey at study end. The relevant question asks, "Which are you more likely to use to monitor your symptoms" and has 2 mutually exclusive options for an answer: "An activity tracker" or "A mobile phone app." This outcome directly tests the hypothesis that BP individuals prefer activity trackers over mobile phone apps for monitoring their symptoms. Adherence rate for activity tracking is measured as the proportion of study days with at least 12 hours of activity tracking, which is determined indirectly using total minutes Fitbit measures heart rate. Adherence rate for self-reporting symptoms is measured as the proportion of study days with at least 50% of daily self-reports survey questions completed.

The second and third outcome tests the hypothesis that reviewing collected data weekly will increase engagement in monitoring symptoms. The second outcome is *difference in adherence rates for self-reporting symptoms between individuals who review their data weekly with an interviewer (Arm R) compared with individuals who do not review their data weekly with an interviewer (Arm NR).* The third outcome is *difference in*

adherence rates for activity tracking between individuals who review their data weekly with an interviewer (Arm R) compared with individuals who do not review their data weekly with an interviewer (Arm NR).

To accompany these measures of adherence and engagement, we will also use other responses on the engagement survey to further examine reasons why an individual might monitor their symptoms with either a mobile phone or an activity tracker. Since responses are in the form of multiple-choice options, we will report number and proportion of participants in the entire group and in each arm, who choose each option.

Secondary Outcome Measures

Secondary outcome measures evaluate whether symptoms improve in the study: change from baseline in severity of manic symptoms, as measured with the YMRS; and change from baseline in severity of depressive symptoms, as measured with the 17-item SIGHD. We hypothesize that by tracking symptoms throughout the study, individuals with BP improve their symptoms. Establishing validity of this hypothesis will serve to reinforce the importance of monitoring symptoms in BP as a target in therapy.

Exploratory Aims

Along with evaluating primary and secondary measures above, the data collected from this study provides opportunities to examine other questions. For one, we want to establish validity of our mobile-based 6-item survey for tracking BP, by determining to what extent the 6 symptoms can explain total scores on the weekly interview-based YMRS and SIGHD total scores as was demonstrated in our preliminary analysis. Additionally, we want to examine other strategies for increasing engagement in monitoring BP symptoms. To that end, we will examine responses on our engagement survey about providing charts and graphs of user data over time, top 3 uses of

technology for monitoring symptoms, top 3 barriers of preventing technology from being used to monitor symptoms, and top 3 symptoms or patterns to monitor. Finally, we want to evaluate mathematical models for personalizing phenotypes of BP based on *daily* patterns of mood in BP [11].

Statistical Tests

For the first two primary outcome measures, we will test whether proportions are statistically different from 0.5 using a binomial test. These tests answer whether users prefer and adhere to monitoring symptoms using apps over activity trackers. For the second two primary outcome measures, we will test whether adherence rates are statistically different between arms using a 2-sample Student *t*-test if variances can be assumed to be equal, otherwise a Welch *t* test will be used. These tests answer whether users better adhere to monitoring symptoms with apps and activity trackers when reviewing collected information weekly with an interviewer. For the secondary outcome measures, we will test whether individuals experience a statistically significant increase in YMRS and SIGHD scores from baseline over the course of the 6-week study using McNemar test, which compares the number of individuals whose survey scores increased versus those whose survey scores decreased. For all statistical tests, significance will be considered a *P* value less than .05.

Results

We began recruiting for this study on November 27, 2017. As of January 1, 2018, we had 3 people enrolled and consented in the study. Study participations began in January 2018. The study app was released to Google Play and iTunes in Fall 2017 but is currently password-protected to restrict use to study participants.

Discussion

Principal Findings

We presented a study on engaging individuals with BP in self-monitoring symptoms with a mobile phone app and activity tracker. Individuals with BP are characterized by extreme shifts in their mood ranging from mania to depression, which often arise quickly and without warning. The WHO recommends that individuals with BP monitor their symptoms [8], and many psychosocial interventions in BP include some form of monitoring symptoms to provide early warnings, raise awareness of symptoms, and provide insight into an individual's illness

[2]. Perhaps most importantly, monitoring of symptoms is a minimum requirement to determine effective adaptive interventions that deliver the *right* psychosocial interventions to the *right* individual at the *right* moment [14]. Making it easier to monitor symptoms is the promise of mobile and wearable technology, mirroring a larger trend for chronic diseases such as BP.

Our goal is to ensure that such technology is optimally designed and evidence-based for monitoring symptoms in BP. We thus focus on formally testing 3 engagement strategies: using activity trackers rather than self-reports in a mobile phone app; reviewing collected information weekly; and synthesizing information with charts and graphs. We expect to verify that the individuals with BP prefer and better adhere when using activity trackers over self-reports in a mobile phone app to monitor their symptoms, and when information is reviewed weekly. We also expect that individuals with BP, in the study, will experience a decrease in manic and depressive symptoms, reinforcing the idea that monitoring symptoms can alone be therapeutic and can provide further impetus for individuals with BP to monitor their symptoms. Our study app was simple in its design: users can log, review, and visualize their mood. This simplicity ensures study results will generalize to the wealth of mobile and wearable technology developed for BP [15-20,22,23], translating into better technology for individuals with BP for monitoring symptoms.

Limitations

We remark on two limitations of the study design. First, we do not track usage statistics other than whether a participant logs their symptoms. Specifically, we do not track whether a participant logs their symptoms through a mobile phone app or online, which would be useful in understanding how individuals monitor their symptoms. Second, we provide participants a Fitbit at the start of the study, which many have never used before. Introduction of the activity tracker may influence engagement. For some individuals, we expect engagement in the study to be higher than long-term engagement because of the novelty of the tracker. For others, we expect engagement in the study to be lower than long-term engagement because they are not familiar with the device. For example, we find that certain individuals do not sync their Fitbit on a regular basis. To help estimate long-term engagement, we thus ask in our engagement survey how long individuals would continue to use the activity tracker.

Authors' Contributions

ALC designed the study and drafted the manuscript. ALC and LVB-W designed the study app. MGM coordinated the study and provided data for initial analyses. All authors read and approved the final version of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Informed Consent document.

[PDF File (Adobe PDF File), 178KB - resprot_v7i5e130_app1.pdf]

Multimedia Appendix 2

Detailed protocol for the study.

[PDF File (Adobe PDF File), 168KB - resprot_v7i5e130_app2.pdf]

Multimedia Appendix 3

Engagement survey: a 17-item survey to be administered over the phone at the end of the study and to assess engagement of participant in self-monitoring of symptoms. Items ask about general feelings and attitudes toward using mobile and wearable technology to monitor symptoms.

[PDF File (Adobe PDF File), 49KB - resprot_v7i5e130_app3.pdf]

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Abbreviations

BP: bipolar disorder
NIMH: National Institute of Mental Health
SIGHD: Structured Interview Guide for the Hamilton Rating Scale of Depression
SF-36: 36-Item Short Form Health Survey
YMRS: Young Mania Rating Scale

Protocol

A Self-Directed Mobile Intervention (WaznApp) to Promote Weight Control Among Employees at a Lebanese University: Protocol for a Feasibility Pilot Randomized Controlled Trial

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Abstract

Background: Overweight and obesity have become major health problems globally with more than 1.9 billion overweight adults. In Lebanon, the prevalence of obesity and overweight is 65.4% combined. Risk factors of obesity and overweight are preventable and can be addressed by modifications in the environment and in an individual's lifestyle. Mobile technologies are increasingly used in behavioral, self-directed weight management interventions, providing users with additional opportunities to attain weight control (weight loss, weight gain prevention, etc). Mobile apps may allow for the delivery of Just-in-Time Adaptive Interventions (JITAIs), which provide support through skill building, emotional support, and instrumental support, following the participants' progress. A few commercially available apps offer JITAI features, but no studies have tested their efficacy.

Objective: The primary objective of this study is to examine the feasibility of a self-directed weight loss intervention, targeting employees of an academic institution, using a virtual coaching app with JITAI features (Lark) and a self-help calorie-counting app (MyFitnessPal). The secondary objective is to estimate the effects of the intervention on main study outcomes.

Methods: This study is a single-center, parallel, randomized controlled trial with 2 study arms (intervention and control). Participants will be randomly allocated in equal proportions to the intervention (Lark) and control groups (MyFitnessPal). To be eligible for this study, participants must be employed full- or part-time at the university or its medical center, able to read English, have a smartphone, and be interested in controlling their weight. Recruitment strategies entail email invitations, printed posters, and social media postings. We will assess quantitative rates of recruitment, adherence, and retention, self-reported app quality using the user version of the Mobile App Rating Scale. We will also assess changes in weight-related outcomes (absolute weight and waist circumference), behavioral outcomes (physical activity and diet), and cognitive factors (motivation to participate in the trial and to manage weight).

Results: WaznApp was funded in June 2017, and recruitment started in March 2018.

Conclusions: This study will provide information as to whether the selected mobile apps offer a feasible solution for promoting weight management in an academic workplace. The results will inform a larger trial whose results might be replicated in similar workplaces in Lebanon and the Middle East and North Africa region, and will be used as a benchmark for further investigations in other settings and similar target groups.

Trial Registration: ClinicalTrials.gov NCT03321331; https://clinicaltrials.gov/ct2/show/NCT03321331 (Archived by WebCite at http://www.webcitation.org/6ys9NOLo5)

KEYWORDS

mobile apps; weight loss; physical activity; healthy diet; workplace; mHealth; randomized controlled trial

Introduction

Background

Noncommunicable diseases (NCDs), also known as chronic diseases, are one of the major global public health challenges of the 21st century, being responsible for about 40 million deaths per year, 15 of which are premature (ie, between 30 and 69 years) [1]. The majority of these deaths occur in low- and middle-income countries (LMICs). According to the World Health Organization's (WHO's) global report, cardiovascular diseases, cancer, diabetes, and chronic respiratory diseases are responsible for 82% of all NCD deaths [2]. In Lebanon, the prevalence of NCDs accounts for 85% of all deaths. NCDs are the product of 4 main risk factors: tobacco use, physical inactivity, the harmful use of alcohol, and unhealthy diets, which, in turn, lead to 4 key metabolic changes (raised blood pressure, overweight and obesity, raised blood glucose, and raised cholesterol) [1]. With regard to overweight and obesity, globally, in 2014, there were more than 1.9 billion overweight adults, representing 39% of the world population. Of these, 600 million were obese [3]. In Lebanon, the prevalence of obesity and overweight is 65.4% (obesity accounting for 27.4% and overweight for 38%) [4]. A fundamental cause of obesity and overweight is an energy imbalance between caloric intake and caloric consumption. This imbalance is due to global trends of increased availability and intake of energy-dense foods that are high in sugar and saturated fats, and insufficient physical activity, due to the sedentary nature of many forms of work, modes of transportation, and increased urbanization [3]. All these behavioral risk factors are preventable, as they can be addressed by modifications in the environment and lifestyle of individuals (ie, increasing physical activity, reducing sedentary time, and following a healthy diet) [5].

The effectiveness of nonsurgical and behavioral weight management interventions has been demonstrated in several systematic reviews and meta-analyses [6,7]. For example, commercially available weight loss treatments, such as WeightWatchers, and pharmaceutical products, such as Qsymia, were found to be cost-effective strategies to achieve weight loss [8]. Effective behavioral interventions should include both physical activity and dietary components to reach larger and sustained effects [9]. Self-monitoring is one of the most effective change techniques [10] included in behavioral weight loss interventions, as evidence shows that people who report weight monitoring on a daily or weekly basis tend to be more successful in attaining weight loss goals [11,12]. Self-monitoring improves the awareness of caloric and food intake, increases self-efficacy, and permits the evaluation of any change or progress over time [13]. However, long-term weight loss and maintenance interventions that are delivered face-to-face usually require substantial work of a specialist workforce and sizeable resources, both from the participants and the service providers.

In the past decade, "health services and information delivered or enhanced through the internet and related technologies" (ie, "eHealth") [14] have transformed the way patients interact with the health care system [15] and engage with their own health [16]. eHealth technologies allow users to monitor, track, and inform their health; communicate between health agencies and external stakeholders in terms of health; and collect, manage, and use health data [17]. In this context, new strategies for behavioral weight management interventions have been developed [18-22], with the aim to provide users with the support necessary to attain weight loss and, at the same time, contain costs [23]. The potential of eHealth and mobile health (mHealth) is especially relevant to LMICs, where phone ownership is rising rapidly, but access to health care services is often limited. Recent systematic reviews on eHealth behavioral interventions addressing NCDs and their risk factors in LMICs show promising results [24,25]. The attention toward mHealth apps is also justified by the high penetration rates of these technologies. According to a 2014 Pew Research Center survey, in Lebanon, the penetration rate of mobile phones was 86%, with smartphones reaching 45%, the highest penetration rate in the Middle East and North Africa (MENA) region [26]. Smartphone ownership is as high as 60% among adults aged 18 to 29 years and 55% among adults aged 30 to 49 years [26]. More recent data (October 2016 to November 2017) available from Net Marketshare show that mobile and tablet represent 61% of the market in Lebanon, with Android capturing 61% and iOS capturing 38% of the Lebanese market.

Mobile phones, and particularly apps, have been considered convenient intervention platforms as they are portable, appealing, and universal [27]. Mobile phones can be used for self-directed interventions for weight management. Self-directed interventions are those that "require minimal professional contact (eg, provision of initial instructions) or no professional contact and can be easily used with existing infrastructure and in the context of users' everyday lives" [28]. Mobile apps started to show some suggestive evidence of effectiveness [18,29], with studies reporting positive effects in weight reduction when apps were employed as a supplement to telephone coaching [30]. However, small, nonsignificant effects were reported when apps were used as a standalone tool [31,32]. Smartphones are the ideal platform for delivering self-directed, Just-in-Time Adaptive Interventions (JITAIs), which are treatment programs that, as the name suggests, adapt to the patients' progress, eg, when they attain goals or positively respond to treatment [33]. JITAIs can provide support through skill building (coping, making decisions, planning, etc), emotional support (encouragement, etc), and instrumental support (feedback, etc) when users need these features the most [33,34]. JITAIs are complex,

algorithm-dependent interventions based on several design principles, which include decision points and outcomes that would inform the provision of tailored feedback (ie, tailoring variables), intervention options (based on *if-then* conditions grounded on behavioral theories, aimed at addressing short-term behavioral outcomes), and decision rules. For a more detailed overview of the JITAI framework, we refer the reader to the seminar report by Nahum-Shani et al [34]. Mobile devices are adequate platforms for delivering feasible and scalable JITAIs, given the smartphone technology advancements that are providing users with continuous monitoring and personalized coping strategies [34]. Nevertheless, little is known about the efficacy of mobile apps acting as main components of JITAIs for weight management.

According to the WHO's global action plan for the prevention and control of NCDs [35], workplaces are one of the most important settings for health promotion as they are the gateway to a large number of people (about 65% of the world's population is employed) [36]. In the last two decades, many public health efforts have been made, and numerous interventions have been conducted to tackle these problems. There is a wide evidence supporting the effectiveness of workplace interventions for the prevention of obesity [37-40], and many national governments adopted policy decisions for promoting health through workplaces. In response to the WHO call for action, the Lebanese Ministry of Public Health released a plan for the prevention and control of NCDs in 2016 [4], which provides a set of guidelines for action, despite excluding workplaces as a setting for priority interventions. This gap is being filled by the American University of Beirut (AUB) and its Medical Center (AUBMC) [41], which have expressed their commitment toward building a healthier campus and community through a long-term strategic plan endorsed in the Health 2025 vision.

Aims of This Study

The overarching goal of this study is to determine the feasibility and preliminary efficacy of a self-directed weight management intervention, targeting university employees and delivered entirely through mobile apps. Specifically, the study aims to (1) evaluate the acceptability and feasibility of using 2 commercially available mHealth apps for weight management; (2) evaluate the feasibility of implementation strategies, retention, and adherence to the study, fidelity to the protocol, assessments, and data collection procedures; and (3) estimate the effects of the interventions on weight-related outcomes (eg, weight, body mass index, and waist circumference), as well as on behavioral (physical activity and diet), and cognitive factors related to weight loss (motivation to lose weight, to engage in physical activity, and follow a healthy diet).

Methods

Participants and Procedures

Participants are employees working at AUB and its Medical Center (AUBMC), located in Beirut, Lebanon. Employees include faculty (n=1182), of which 41.03% (485/1182) are female; nonacademic staff at AUB (n=1266) of which 46.99% (595/1266) are female; and AUBMC staff (n=3038) of which

52.00% (1580/3038) are female [41]. The employer did not influence the design of the study or its methodology. The recruitment strategy does not rely on the endorsement of any AUB or AUBMC authorities. Participants will be informed orally and through written consent forms that their participation is completely voluntary, free of charge, and no penalty will be pressed for those not willing to participate.

To be enrolled in the study, participants must (1) be employed full- or part-time; (2) be able to read, write, and understand English; (3) own a smartphone with either Android (v4.4 or above) or iOS (v8 or later); and (4) be interested in better controlling their weight (ie, losing weight, preventing weight gain, maintaining weight lost, or gaining weight in a healthy way). Exclusion criteria include the following: (1) being full-time students who cannot prove their status as full- or part-time employees at AUB or AUBMC; (2) not being able to read, write, and understand English; (3) not owning a smartphone with either Android (v4.4 or above) or iOS (v8 or later); (4) having physical disabilities preventing from exercising or walking; (5) being on a special diet for treatment of chronic conditions (eg, diabetes); (6) being diagnosed with anorexia or bulimia nervosa; (7) being on weight loss medications; and (8) having undergone bariatric surgery in the past 3 months. The trial is registered at ClinicalTrials.gov [NCT03321331]. The protocol of this study has been approved by the local Institutional Review Board (ref #FHS.MB.07/SBS-2017-0416).

Recruitment and Randomization

Participants will be recruited through email invitations sent from the AUB Health and Wellness Center, and printed posters hanged on billboards on campus. A digital version of the poster with a shortened link (bit.ly/WaznApp) and QR-code linking to an eligibility screener survey will be displayed on monitors on campus TV screens. Invitations to enroll will also be circulated on social media using the research team's personal and professional social networks (Facebook, Twitter, LinkedIn, and ResearchGate). Emails, posters, and social media postings will contain a link leading to an eligibility screener survey, which will first display an informed consent form. The survey, designed using LimeSurvey, is hosted on AUB servers. At the end of the form, employees will be instructed to complete their enrolment by visiting the University Health Services (UHS) clinics, where nurses will verify their eligibility and take basic anthropometric measurements (ie, height, weight, and waist circumference). Nurses will fill out paper-based forms, thereby cross-checking their eligibility to participate in the study. If participants are eligible, nurses will inform the participants that the research team will contact them via email with information about the next steps in the study. Nurses will provide a hard copy of the consent form to all participants.

Randomization procedures will take place after employees are confirmed to be enrolled in the study. A random sequence based on the minimization procedure will be generated using a computer program, following Altman and Bland's approach [42]. The minimization procedure allows to balance the allocation of study participants to a prespecified number of treatment groups as soon as they enroll in the study, considering participant characteristics (ie, stratification by gender, age, and

anthropometric features) collected during the eligibility phase. The program used to perform the minimization procedure is QMinim [43]. A statistician from the Faculty of Health Sciences will generate the sequence using the program. The random sequence will be uploaded to the REDCap (Research Electronic Data Capture) platform [44]. The research team will inform participants about their allocation after the visit, with a welcome email.

As we need to provide intervention participants with a link to download a full version of the app, allocation concealment and blinding cannot be applied. However, efforts will be implemented to reduce allocation bias. First, the clinical staff weighing participants at baseline and Week 12 will be blinded to treatment groups. Second, after the baseline clinic visit and the initial account set-up, minimization procedures will be undertaken by a statistician, not involving the principal investigator. Third, the intervention is completely delivered via mobile apps. The only contact is related to study procedures and data collection. Finally, data analysis will be conducted on masked data.

WaznApp Study Overview

The WaznApp study is part of a larger project entitled "Can commercial mobile apps for weight management be used in interventions? Bridging the gap between usability, theoretical adherence, and user experience." The project included a formative phase, which was based on a user-centered heuristic evaluation study, aimed at understanding how members of the employee community perceive 6 weight management apps (Lark, MyFitnessPal, SparkPeople, MyPlate, My Diet Diary, and My Diet Coach). The 6 apps were selected because they achieved the highest total scores on the Mobile App Rating Scale (MARS) [45], in a recent expert review [46]. In the heuristic evaluation study, 36 employees were randomly assigned to use one of these apps for 2 weeks. At the end of this period, they submitted their app quality evaluation using the user version of the MARS scale (uMARS) [47]. Three apps achieved the highest mean ratings for the total app quality score (Lark=4.0; MyPlate=3.8; MyFitnessPal=3.7). Lark clearly emerged as the app with the highest quality scores. In addition, this app has been recently employed in an observational study, involving 70 diabetic patients, who lost 2.4% of their weight at baseline after about 15 weeks [48]. Users of MyPlate reported several functionality issues, and its database is not as complete and responsive as its popular counterpart MyFitnessPal, which is one of the most downloaded apps for dietary tracking [49]. Compared with another popular app (Lose It!), MyFitnessPal allows users to automatically track activity through the phone or through integrations with many wearable devices [50]. For these reasons, we selected Lark and MyFitnessPal as trial apps.

The WaznApp study is a 12-week, prospective, single-center, parallel, randomized controlled trial with 2 study arms. The intervention arm will use Lark, a mobile coach, which provides interactive counseling through a chat-style interface by delivering motivational feedback, goal setting, and emotional social support. Lark acts as an adaptive intervention [33] and provides feedback on several outcomes (see, eg, the text and

app-based Cell Phone Intervention for You trial [51,52]). The content of the messages depends on the way users interact with the app. The content is based on several behavior change techniques, such as goal setting, reviewing behavioral goals, feedback, and social support [46]. The users input their activities, foods or weight, but the app tracks automatically their active time using proprietary algorithms and phone motion sensors. The control group will use MyFitnessPal, a calorie-counting app that does not include JITAI components and relies on the user input for food tracking. MyFitnessPal acts as the control condition, as it provides limited social support, which is present in Lark, and it is an important feature that is generally lacking in calorie-counting apps [53].

Description of Treatment Arms

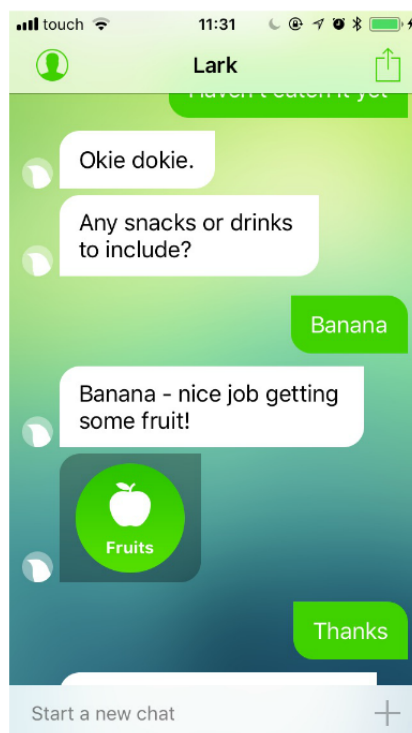### Intervention Arm (Just-in-Time Adaptive Intervention)

Participants in the intervention arm will use Lark Pro for 12 weeks. Lark, developed by Lark Technologies Ltd, is a personal weight management health coach based on artificial intelligence that interacts with the user in a chat-like format. Lark Pro includes a personalized health plan and nutrition coaching, as well as physical activity, weight, sleep, and mood tracking. Once the app is launched, Lark checks the data that the user inputted (ie, food meals; physical activities such as walks, runs, bike, and workouts; and weight) or that was automatically logged through the phone motion sensors (ie, activity, sleep) or external devices (eg, Apple Watch, digital scales). On the basis of this information, Lark generates interactive conversations every time individuals use the app. Conversations about meal logging are geared toward food choices and portions rather than calorie counting; conversations may include messages that provide solutions to problematic situations, fostering action planning and problem-solving skills. The app sends notifications to prompt the users to review their activity throughout the day. Following the behavior change technique taxonomy v1 [10], Lark includes the following techniques: "goal setting" of behavior and outcomes (eg, activity, weight), "review outcome goals," "self-monitoring" of behavior and outcomes, and "feedback" on behavior or on outcomes of behavior (Figure 1). In addition, users may receive "information about health consequences" (eg, when inputting a "muffin" as a meal, the app may respond: "That wasn't the healthiest of meals/When I say this I am referring to the quality of the actual foods rather than taking into account the quantity you eat, but obviously eating an entire dessert is less healthy than having a single taste"). Lark also helps users to develop "problem-solving" skills (Figure 2), providing alternative solutions ("What's a healthier choice?" response: "You could try fruit, which is sweet, filling, and packed with antioxidants"). The app also provides "emotional support" (eg, "know that when it comes to weight loss, ups and downs are typical") and "positive reinforcement" (Figure 3). Sometimes, the app suggests information based on "credible sources," as it has been developed in collaboration with researchers from Stanford and Harvard universities.

In agreement with Lark Technologies, users will utilize an app that will not be updated until the end of the study, to minimize variability in the intervention delivery.

Figure 1. Example of self-monitoring of physical activity and visual feedback on behavior.
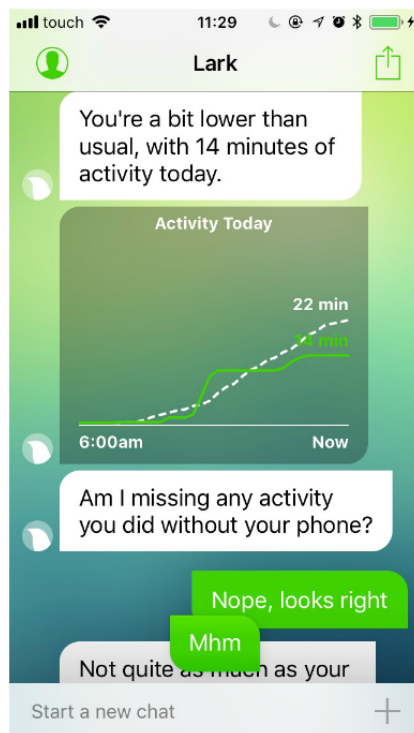
Figure 2. Example of mindful logging with problem-solving skills.
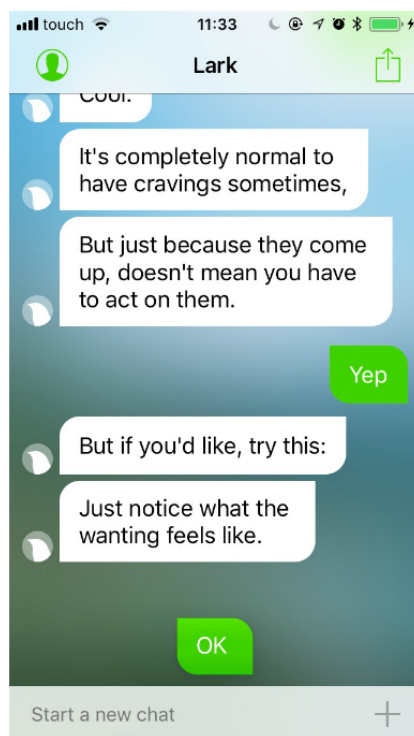
Figure 3. Example of positive reinforcement (ie, "social reward").

Control Arm (No Just-in-Time Adaptive Intervention)

Participants in the control arm will be assigned to use MyFitnessPal. Similar to participants in the JITAI arm, they will be instructed to use the app for 12 weeks. MyFitnessPal does not include JITAI components, but it allows users to keep track of their caloric intake and energy expenditure. According to the previously cited review of mHealth apps for weight management [46], MyFitnessPal also has features that can be associated with effective behavior change techniques, including self-monitoring of behavior and outcomes, goal setting, and feedback (similar to Lark). In MyFitnessPal, social support is limited to comments and "likes" from friends of its restricted user community; hence, it might include "social comparisons" and "social reward" behavior change techniques [10]. MyFitnessPal acts as an active control arm as it relies almost exclusively on self-control, compared with Lark, as the latter provides an emotional social support from the coach, who provides positive enforcement and motivational messages to further encourage behavior change.

Additional Components

This study will be delivered almost entirely through mobile phones. Face-to-face interactions with the research team will be kept at minimum and used only to ensure that the mobile apps have been installed correctly, and there are no issues related to the use of technology during the intervention period. Participants will be instructed via manuals and tutorials delivered via email on how to download and use the apps, complete the surveys, and how to use the food composition tables for use in the Middle East [54], available from the local library. Manuals for completing dietary assessment using the Web-based Automated Self-Administered 24-hour (ASA24) Dietary Assessment Tool, version 2016, are available directly on the tool's website. Emails will be used to communicate with study participants and to send them links for completing Web-based intermediate and follow-up assessments (collected through REDCap). The research team will encourage participants to keep their phone with them to track steps and active time, as the phones automatically collect the number of steps walked using built-in accelerometers.

Incentives for Participation

Study participants will not receive any payment for their participation, but they will be awarded "WaznApp karma points" (WAKpts) for completing tasks related to the study. Karma points are a nonmonetary measure of contribution to the study [55] and are awarded when participants in both intervention groups duly fill the Web-based questionnaires and food records. Each question filled in is worth 1 WAKpt. The points are according to the number of tasks completed. If the participants collect at least 600 points, they will enter the final lottery for Fitbit products, which will take place at the end of the study.

Intervention Administration and Fidelity

The intervention is delivered by the apps in an automated way. Neither the research team nor the developers have direct contact with participants and will not prompt app use. The research team will send emails to participants only to remind them about data collection procedures via REDCap. All research assistants have undertaken Collaborative Institutional Training Initiative training and acquired certification. Nurses collecting data and eligibility information will be trained before the start of the study. The research team will meet the nurses and provide instructions on how to fill the eligibility forms. Intervention fidelity will be monitored weekly, through meetings with research assistants and through the support of a project management platform (Basecamp), which keeps track of activities and tasks. Participants' compliance with the

intervention will be assessed through the email data collection points at baseline and Weeks 4, 8, and 12.

Outcomes

In this study, primary outcomes are those related to the feasibility, whereas secondary outcomes are those related to the preliminary efficacy. The timeline for data collection is specified for each outcome below. We will collect data mostly through mobile-friendly, Web-based surveys. Participants will be invited to fill the questionnaires via email, which will contain personalized links to the surveys. Before the start of the study, all instruments will be pilot tested.

Feasibility and Acceptability Outcomes

As done in other similar trial [56], feasibility measures include quantitative rates of recruitment, adherence, and retention. Adherence to the study will be based on the number of data collection points completed and on qualitative feedback related to the study requirements. For Lark users (intervention group), we will use the logs of the app about quality (ie, detail and accuracy) and quantity of meals logged, daily activities logged, weight, sleep duration, and the number of conversations with the Lark coach as measures of intervention adherence. Retention rates will be calculated at the end of the study based on the number of participants who successfully complete the study, excluding dropouts. For both intervention and control groups, we will ask participants to provide information about their weekly app usage (hours/week). In Week 4, 8, and 12 surveys, we will add instructions on how to find the information on iPhones, using the built-in battery saving analytics, or Android phones, using the free app called *Frequency: App Usage Tracking*.

Acceptability of the trial will be assessed using qualitative feedback collected at each data point through open-ended questions (ie, "What are your major concerns about the study procedures, if you have any?"; "What are your major concerns about the app you have used?"; "What are your major concerns about the questionnaires?" Please elaborate your answers in the box below). Satisfaction with the program will be assessed through a 7-point rating scale (semantic differential), ranging from extremely satisfied to extremely dissatisfied. An open-ended question will give participants the option to elaborate on their response. These measures are calculated at the end of the study (Week 12). Satisfaction with the app will be assessed through the uMARS [47]. The uMARS scale provides a measure of app quality based on the average of 4 subdomains: engagement, functionality, aesthetics, and information; it also includes the subjective quality domain. Each of the subdomains is based on the average value of multiple items, assessed through 5-point Likert scales (engagement: 5 items; functionality and information: 4 items; aesthetics: 3 items; and subjective quality: 4 items). In the uMARS developmental study [47], the total scale and subscales achieved good and excellent internal consistency: engagement (Cronbach alpha=.80); functionality (alpha=.70); aesthetics (alpha=.71); information (alpha=.78), total (alpha=.90), and subjective quality (alpha=.78). As the uMARS tool requires that users utilize the app before rating it, app quality will be collected at Weeks 4, 8, and 12 (to allow for test-retest reliability estimates).

Secondary Outcomes

Secondary outcome measures include changes in weight-related outcomes (absolute weight and waist circumference), behavioral outcomes (physical activity and diet), and cognitive factors (motivation to participate in a weight management program). Absolute weight and waist circumference will be measured with standard instruments and procedures at baseline and Week 12 by assessors blinded to arm allocation from AUBMC UHS. Intermediate self-reported measures of weight will be based on weekly check-ins, automatically prompted by the mobile apps, and collected through Web-based forms at Weeks 4 and 8.

Activity information will be captured through the phones, which will be integrated with *Google Health Kit, Apple Health*, or Samsung S Health. Participants will be asked to read and report average weekly measures of steps walked and weekly active time at Weeks 4, 8, and 12. Lark automatically tracks the amount of active time per day, whereas MyFitnessPal can estimate the number of steps walked using the phone accelerometer or external, third-party devices such as Fitbit, Misfit, and Apple Watch. As not everyone may have their phone with them all the time, we will assess physical activity also through the International Physical Activity Questionnaire, short form (IPAQ-S) [57]. IPAQ-S is one of the most widely adopted self-reported instruments to assess physical activity, which has been designed to be easily used in many languages and countries [58]. Despite the limitations of self-reported instruments compared with objective methods for measuring physical activity (eg, the "gold standard" doubly labeled water), the IPAQ-S is a feasible, easy-to-use instrument to capture physical activity [58]. As there was no budget for more reliable physical activity assessment instruments (eg, Actigraph accelerometers or pedometers), we chose the IPAQ-S because of its ease of use, as it is perceived as less daunting than the long form showing similar reliability and validity estimates [59]. Furthermore, the IPAQ-S tool has been previously used in epidemiological studies in Lebanon [60,61]. The IPAQ-S requires respondents to estimate how much time they spent while doing activities in the previous week in 4 domains: vigorous physical activity, moderate physical activity, walking, and sitting. A total physical activity score is calculated by summing the time spent in each domain. The total physical activity score and subdomain scores can be expressed in hours/week, or converted to metabolic equivalents (METs), following the IPAQ scoring protocol [62]. MET values were derived from the IPAQ Reliability Study [59], and an average MET score will be derived for each type of activity using the compendium of Ainsworth et al [63]: 1 MET equals the energy expenditure of sitting down quietly, 3.5 ml O_2/kg/min. Physical activity will be assessed through the IPAQ-S questionnaire at baseline and Week 12.

Dietary intake data will be collected and analyzed using the Automated Self-Administered 24-hour (ASA24) Dietary Assessment Tool, version 2016, developed by the National Cancer Institute, Bethesda, MD. ASA24-2016 is based on the Automated Multiple-Pass Method, developed by the United States Department of Agriculture [64]. The multiple-pass approach in 24-hour recall provides a detailed assessment of dietary intake over the past 24 hours, including food, drinks,

and supplements, as well as timing, form, portion size, the way food has been prepared, and the consumption of additions such as sugar, cream, and dressing, in addition to the source/brand of food. The 2016 version of the system includes also pictures of portions that are deemed to reduce overestimation or underestimation of food intake [65]. Since its release date (April 2016), ASA24-2016 has been used in 882 studies and 37,090 recalls have been completed. Various versions of ASA24 have also been used in self-directed weight loss interventions [66-68]. The automated version of ASA24 generally showed good reliability compared with the interviewer-administered version [69] or with the measures of true intake [70]. The ASA24-2011 version has been validated against and shown close agreement with interview-administered 24-hour dietary recalls among adults and children [70,71]. In this study, participants will complete an ASA24 at baseline and at the end of the intervention. The ASA24-2016 will be used on 3 nonconsecutive days (2 in a week day and 1 in a weekend, eg, Mondays, Thursdays, and Saturdays). Participants will access the Web-based ASA24 platform where they will be asked to recall food, drinks, or supplements they consumed in the last 24 hours. The questionnaire can be accessed via mobile phones, as it uses a responsive Web interface. Energy and macronutrients estimates will be computed using the Nutritionist Pro Software, using the United States Department of Agriculture (USDA) database (version 5.1.0, 2014, First Data Bank, Nutritionist Pro, Axxya Systems, San Bruno, CA). For composite dishes or items that are not included in the USDA database, traditional recipes will be added to the Nutritionist Pro Software, using single food items. ASA24-2016 will be assessed at baseline and Week 12. Calorie intake using the apps will be prompted at Weeks 4, 8, and 12.

Motivation to participate in a weight management program is one of the key elements of its success [72]. This construct will be assessed using the Treatment Self-Regulation Questionnaire (TSRQ) [72-74]. TSRQ includes autonomous and controlled regulation subscales. Motivation to participate in the program will be assessed at baseline and Weeks 4, 8, and 12. Additionally, stages and processes of change in weight management will be assessed using the S- and P-Weight scales [75,76]. The S- and P-Weight scales assess the cognitive predictors of weight change [77]. These scales are based on the transtheoretical model and include stages of change (S-Weight) and processes of change (P-Weight) components to assess the motivation to lose weight, which can be considered both a moderator and a mediator or covariate factor in achieving the main outcome (ie, weight loss). Stages and processes of change will be assessed at baseline and Week 12.

Data Collection and Management

Except for the 24-hour recall/record done through the Web-based ASA24 platform, process and outcome measurements will be collected through REDCap [44], which is a secure, the Health Insurance Portability and Accountability Act compliant, Web-based survey application hosted on AUB servers. REDCap is an ideal program for managing longitudinal studies with multiple assessments.

Sample Size

Traditional sample size calculations are not typically undertaken in nonprobability sampling and in pilot interventional studies, as these are intended to test acceptability and evaluate the process as well as to inform power calculations for subsequent studies [78]. Nevertheless, researchers recommend that sample size justifications are provided also in pilot studies [78]. In the absence of similar studies in Lebanon and in the region, it is difficult to estimate precise effect sizes. However, estimates can be derived from the average effect sizes reported in similar mobile-based weight loss interventions that had minimal researcher interaction [79-81], included in Schippers et al's meta-analysis [21]. In these studies, the effect sizes (SMD, standardized mean difference) based on weight change ranged from d=0.33 [79] to 0.37 [80]. According to Whitehead et al's tables (for SMD=0.3 and 0.4, respectively) [78], a two-arm trial, designed with 90% power and two-sided 5% significance, will require between 305 and 181 participants per arm; a pilot study will require, respectively, 45 and 33 participants per arm [78].

Data Analyses

Descriptive statistics will be conducted for the overall characteristics of the study population through presenting the numbers and percentages for nominal or categorical variables and means and standard deviations for continuous ones. For variables assessed using multiple items (eg, uMARS scales), Cronbach alpha and corrected item-total correlations coefficients will be used to assess the internal consistency of the measured constructs, before aggregating the information (ie, averaging). Bivariate correlations and chi-square tests will be used to explore associations among demographic and psychographic variables and main study outcomes.

Missing data are expected to be minimal for most variables. Depending on the number of participants, the number of missing data points, and the distribution of the outcome variables, we will decide which missing data strategy to use (eg, full-information maximum likelihood or multiple imputation) [82]. The missing data bias will be assessed by computing a binary variable reflecting the presence or absence of missing data for each variable in the model, and then, this binary variable will be correlated with all other variables in the model as well as an array of demographic variables.

Reliability of the uMARS scales will be evaluated using both indices of interrater agreement (IRA) and interrater reliability (IRR) [83-85]. Following the recommendations from the literature [86,87], IRA will also be measured according to Brown and Hauenstein's aWG index [88], and the adjusted average deviation index ADM (adj) [89]. IRR indices will be based on intraclass correlation coefficients measuring test-retest reliability [90,91]. Similarly, test-retest reliability estimates will be used with the ASA24 Dietary Assessment Tool and the IPAQ-S [57].

Independent samples t tests, one-way analysis of variances (or nonparametric alternatives where appropriate) will be used to test differences in the relevant outcome variables (behavioral, cognitive, and weight-related data) between intervention groups and between pre- and posttest. Behavioral and weight-related data will be presented using appropriate confidence intervals

as suggested by Lee and colleagues [92]. The estimation of preliminary efficacy will be based on the observed trends on data over time rather than traditional inferential statistics [93]. Subgroup analyses will also include intent-to-treat versus randomized analyses to detect whether differences in the outcomes are associated with adherence to the trial (per protocol).

Results

Funding for WaznApp study has been secured from the AUB, University Research Board. Recruitment started in February and was completed by the end of March 2018; the study will be completed by the end of June 2018. Data analyses and write-up will start over the summer and be completed by the end of 2018. Any changes in the procedures related to recruitment, eligibility criteria, outcomes, and analyses will be implemented and communicated to study participants via email within 2 weeks from the modifications in the protocol. Results will be communicated in a final report for participants.

Discussion

This study contributes to the growing evidence on mobile apps for weight management [18,19]. The findings of this project will provide information on the feasibility of using commercially available, popular mobile apps as a standalone delivery mode for self-directed interventions for weight management. Furthermore, this study will provide preliminary insights into the potential acceptability and efficacy of an app that acts as a JITAI (Lark) at promoting weight management compared with a non-JITAI, calorie-counting app (MyFitnessPal). Lark has recently been used in an observational study, involving 70 diabetic patients who lost 2.4% of their weight at baseline after about 15 weeks [48]. MyFitnessPal has been utilized in a few weight loss trials, showing some positive effects in weight reduction when employed as a supplement to telephone coaching [30], but small, no significant effects when used as a standalone tool [31,32]. We hypothesize that the use of Lark will be associated with larger, more positive changes in cognitions, behaviors, and anthropometric measures than the other apps. This hypothesis will be tested in a larger trial. In fact, this feasibility study will be used to inform a subsequent trial with the same target population. The results of the larger study may inform other studies targeting similar workplaces in Lebanon and the MENA region, and may be used as a benchmark for further investigations in other settings and with other target groups.

Anticipated limitations of this study include slow recruitment and participation rates; the use of self-reported data, including app usage and activity; and using Web-based questionnaires that might not capture real-life hurdles and potential reasons for failure. Budgetary limitations did not allow us to include more objective measures of physical activity and dietary behaviors and a comprehensive qualitative evaluation of the trial. Nonetheless, this trial will provide information about low-cost, mobile solutions to help employees self-manage their weight.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report.

[PDF File (Adobe PDF File), 87KB - resprot_v7i5e133_app1.pdf]

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Abbreviations

ASA24: Automated Self-Administered 24-hour
AUB: American University of Beirut
AUBMC: American University of Beirut Medical Center
IPAQ-S: International Physical Activity Questionnaire, short form
IRA: interrater agreement
IRR: interrater reliability
JITAI: Just-in-Time Adaptive Interventions
MARS: Mobile App Rating Scale
MET: metabolic equivalent
MENA: Middle East and North Africa
mHealth: mobile health
NCD: noncommunicable disease
TSRQ: Treatment Self-Regulation Questionnaire
UHS: University Health Services
uMARS: user version of the MARS Scale
WAKpt(s): WaznApp Karma Point(s)
WHO: World Health Organization

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Protocol

The Effects of Implicit and Explicit Motor Learning in Gait Rehabilitation of People After Stroke: Protocol for a Randomized Controlled Trial

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Abstract

Background: A significant part of neurological rehabilitation focuses on facilitating the learning of motor skills. Training can adopt either (more) explicit or (more) implicit forms of motor learning. Gait is one of the most practiced motor skills within rehabilitation in people after stroke because it is an important criterion for discharge and requirement for functioning at home.

Objective: The aim of this study was to describe the design of a randomized controlled study assessing the effects of implicit motor learning compared with the explicit motor learning in gait rehabilitation of people suffering from stroke.

Methods: The study adopts a randomized, controlled, single-blinded study design. People after stroke will be eligible for participation when they are in the chronic stage of recovery (>6 months after stroke), would like to improve walking performance, have a slow walking speed (<1 m/s), can communicate in Dutch, and complete a 3-stage command. People will be excluded if they cannot walk a minimum of 10 m or have other additional impairments that (severely) influence gait. Participants will receive 9 gait-training sessions over a 3-week period and will be randomly allocated to an implicit or explicit group. Therapists are aware of the intervention they provide, and the assessors are blind to the intervention participants receive. Outcome will be assessed at baseline (T0), directly after the intervention (T1), and after 1 month (T2). The primary outcome parameter is walking velocity. Walking performance will be assessed with the 10-meter walking test, Dynamic Gait Index, and while performing a secondary task (dual task). Self-reported measures are the Movement Specific Reinvestment Scale, verbal protocol, Stroke and Aphasia Quality of Life Scale, and the Global Perceived Effect scale. A process evaluation will take place to identify how the therapy was perceived and identify factors that may have influenced the effectiveness of the intervention. Repeated measures analyses will be conducted to determine significant and clinical relevant differences between groups and over time.

Results: Data collection is currently ongoing and results are expected in 2019.

Conclusions: The relevance of the study as well as the advantages and disadvantages of several aspects of the chosen design are discussed, for example, the personalized approach and choice of measurements.

Trial Registration: Netherlands Trial Register NTR6272; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6272 (Archived by WebCite http://www.webcitation.org/6ytA937m5)

Registered Report Identifier: RR1-10.2196/9595

Introduction

Background and Rationale

For most people, walking is a motor skill that generally takes place without too much effort. However, for people who have suffered a stroke, walking is often suddenly impaired, which can lead to major consequences in daily life functioning. People may experience impaired walking patterns with lower walking speeds, which has been associated with lower levels of functional ambulation [1]. Gait training is one of the main components of physiotherapy within stroke rehabilitation because it is an important criterion for discharge and requirement for functioning at home [1,2]. Evidence suggests that even in later (chronic) stages after stroke, people are still able to improve motor performance [3]. Many different techniques and therapies can be used to improve walking performance [4]; the challenge for physiotherapists is to choose and deliver gait training in the most efficient and effective manner. Moreover, preferably, obtained improvements in performance are durable over a longer period and resilient under different circumstances and in dual-task situations, for example, walking and talking. Despite the availability of new training approaches such as the use of robotics [5], virtual reality, for example through exergames [6,7] or body weight support training [8], overground walking [9] still seems one of the most applied gait-training approaches in clinical practice. The current literature and clinical guidelines encourage the use of context- and task-specific treatment approaches, an example of which is overground walking [4,10].

To apply overground gait training, physiotherapists are encouraged to use general motor learning principles [10]. Within the context of motor learning, a broad distinction between implicit and explicit motor learning has been described [11,12]. Explicit motor learning can be defined as learning generated by verbal knowledge of movement performance; it involves cognitive stages within the learning process and is dependent on working memory involvement [13]. The definition indicates that the learner is aware of all the underlying facts and rules of the to-be-learned motor skill during the process of learning. In practice, verbal explicit instructions are frequently used, and often these instructions encourage patients to be aware of their own body movements [14]. For example, in gait training, therapists tell patients to think about their performance, for example, "Move your hips to the left and straighten your knee before stepping" [14].

In contrast to explicit learning, implicit motor learning progresses with no or minimal increase in the verbal knowledge of movement performance (eg, facts and rules) and without awareness [13]. Learning is suggested to take place more automatically and in a less conscious manner. The learner is aware of the process of learning but cannot recall the underlying facts and rules of the motor skill. Gait training could be facilitated more implicitly, for example, when a physiotherapist would gradually constrain or change the environment, for example, when letting the person walk over different surfaces.

In this situation, verbal instructions are not needed, but the environment facilitates the motor skill (walking). An observational study demonstrated that often multiple learning strategies are being used within one training session [15]. These different learning strategies may represent an implicit-explicit continuum on which some promote more implicit and others more explicit forms of learning [11]. Looking at the current practice, therapists seem to have a preference for learning approaches that are related to explicit learning in which often high numbers of verbal explicit instructions are used [14].

Various advantages of implicit motor learning over explicit motor learning have been reported in literature [12]. Studies have demonstrated that individuals who learned motor skills implicitly perform the motor skill better under pressure, perform better in dual-task situations, and perform better over time compared with their explicit counterparts [12,16,17]. Although these studies have primarily been conducted within the healthy population, implicit learning may also be advantageous for the patient population [18,19]. For example, implicit motor learning may be of extra benefit to those with cognitive deficits [20]. Reduced cognitive function is frequently seen in people after stroke [21] and it often hampers the process of motor learning. The degree by which these cognitive functions are being evoked can be influenced by the choice of learning approaches [20]. An interesting feature of implicit motor learning is the assumption that it is less reliant on working memory resources, that is, it involves less cognitive functions, compared with explicit motor learning [19]. It is, therefore, intriguing to explore the effects of implicit motor learning within the stroke population.

Although from a theoretical perspective, the features of implicit motor learning have been described, its practical application in clinical practice seems more complex. Various learning strategies, for example, dual task, or errorless learning have been shown to promote implicit motor learning [17,22]. One learning approach that may also be placed more on the implicit side of the implicit-explicit continuum is analogy learning. In analogy learning, the learner is provided with one single analogy or metaphor that strives to combine all the relevant rules of the to-be-learned motor skill. Early studies on analogy learning took place within a sporting context, for example, to learn specific skill techniques in table tennis or basketball [23,24]. A good example in this regard was presented by Lam and colleagues [23]. They used the analogy instruction "Shoot as if you are trying to put cookies into a cookie jar on a high shelf" to teach basketball players to impart backspin on the basketball. At present, there seems an increased interest of its application within different contexts. Analogy studies have been performed with older people [25] in the context of speech therapy [26] and within neurological populations [27,28]. For example, the analogy "imagine as if you are walking over a frozen lake" has been used in gait rehabilitation to facilitate lifting and placing the foot while walking [28]. With regard to gait rehabilitation, small pilot studies have reported that analogies can be used in a feasible manner to facilitate walking performance [27,28]. It

has been reported that the analogy should lead to the desired biomechanical movement and that preferably the analogy should contain a meaningful component to the participant [28,29]. In addition to feasibility, trends toward improved walking performance have been observed following analogy interventions, which demonstrates the potential of analogy learning in clinical practice [27,28]. However, to further establish the effectiveness of analogy learning in clinical gait rehabilitation, larger sample sizes and research designs using a control condition are required.

This study describes the design for a randomized controlled study to assess the effects of implicit motor learning compared with explicit motor learning on walking speed in people suffering from stroke. The concept of analogy learning is used to structure the gait-training sessions within the implicit condition, whereas explicit motor learning is promoted by using extensive verbal instructions and feedback. A process evaluation is embedded to investigate feasibility and fidelity of the applied interventions.

Research Question

The following research question was established to examine the effects of implicit and explicit motor learning in gait rehabilitation of people after stroke: Is a 3-week implicit motor learning walking intervention (analogies) more effective compared with a 3-week explicit motor learning walking intervention (verbal detailed instructions) delivered at home with regard to walking speed in people suffering from stroke?

Methods

Study Design

The study adopts a randomized, controlled, single-blinded study design in people suffering from stroke in the chronic stage of recovery. The study has been approved by the local ethics committee METC-Z in Heerlen, the Netherlands (NL number: NL.60338.096.16, Ethics nr: 17-T-06). After baseline measures, eligible participants will be randomized to the implicit or explicit condition (T0). Outcome assessments will take place directly after the intervention (T1) and again one month later (T2).

Involvement of Client Representatives

Throughout the design and planning of the study, 3 patient representatives were involved in every step of the decision-making process regarding the design and execution of the study. In several consensus meetings, they represented the patient's perspective, particularly with regard to the feasibility aspects of the study design. They were also involved in customizing participant information letters and promotion material for the study.

Population

The study population consists of people who had a stroke and who are living at home. People will be recruited via local private practices, rehabilitation institutes, and a local health-related newspaper. Participants will be included if they had a stroke and want to improve their gait performance. To minimize the chance that improvements occur as a result of spontaneous recovery, only participants who are in the chronic stage of recovery (>6 months after stroke) will be included in the study. To prevent a ceiling effect, people with a low self-selected walking speed (<1.0 m/s) will be invited to participate. Finally, all people should be able to communicate in Dutch and complete a 3-stage command. People are excluded if they are unable to walk a minimum distance of 10 m; have a functional ambulation category score <3; have additional impairments not related to stroke, which influence their gait pattern, for example, severe osteoarthritis or amputation of the lower limb; have additional neurological impairments, for example, Parkinson disease that (severely) influence their walking performance.

Sample Size

The sample size calculation is based on a randomized controlled trial with equal group sizes and "walking speed" (10-meter walking test, 10MWT) as a primary outcome measure [30]. The power is set at beta=.80, the significance level at alpha=.05, and a standard deviation of 0.23 m/s [31]. To demonstrate a significant change in walking speed, the minimal clinically important difference (MCID) is used and set at a minimum change of 0.16 m/s [32,33]. The calculations resulted in a minimum group size of 33 participants per group. Taking into account that 20% (7/33) of participants may be lost during (dropout) and after the intervention (loss to follow-up), this study aims to recruit 40 participants per group.

Randomization, Blinding, and Treatment Allocation

Randomization Procedure

The allocation of participants to the experimental or the control condition will occur based on a computerized randomization program. Block randomization was calculated in block sizes of fours and sixes. The randomization procedure and the randomization scheme will only be available to an independent researcher who will not be involved in the delivery of the interventions or the performance of the measurements.

Blinding

The trained assessors are blind for treatment allocation. The therapists are aware of the treatment condition as they provide the explicit or implicit motor learning condition. The participants will probably also be aware of the treatment they receive; however, they will not be specifically told. The participants will be asked at each assessment not to reveal the details of treatment they received to the blinded assessor.

Training of Therapists and Treatment of Participants

An intervention guideline is developed that outlines how the treatments (implicit and explicit conditions) should be delivered. The main aim of the intervention is to improve the quality of walking performance in people after stroke. The basic principle of the intervention guideline is based on the definitions of implicit and explicit motor learning by Kleynen et al [11]. For the purpose of this study, we strive to create the largest contrast between the conditions as possible. The main characteristics and differences in instructions, and feedback of the practice between interventions are described in Figure 1. Both conditions will always be applied to an extent that is feasible for the participant, and training will therefore always be tailored to the participant's abilities within the given boundaries of the

condition. Similar situations will be adopted in both conditions with regard to the "organization" of the training, for example, use variation in the (analogy) instructions and practice of the motor skill.
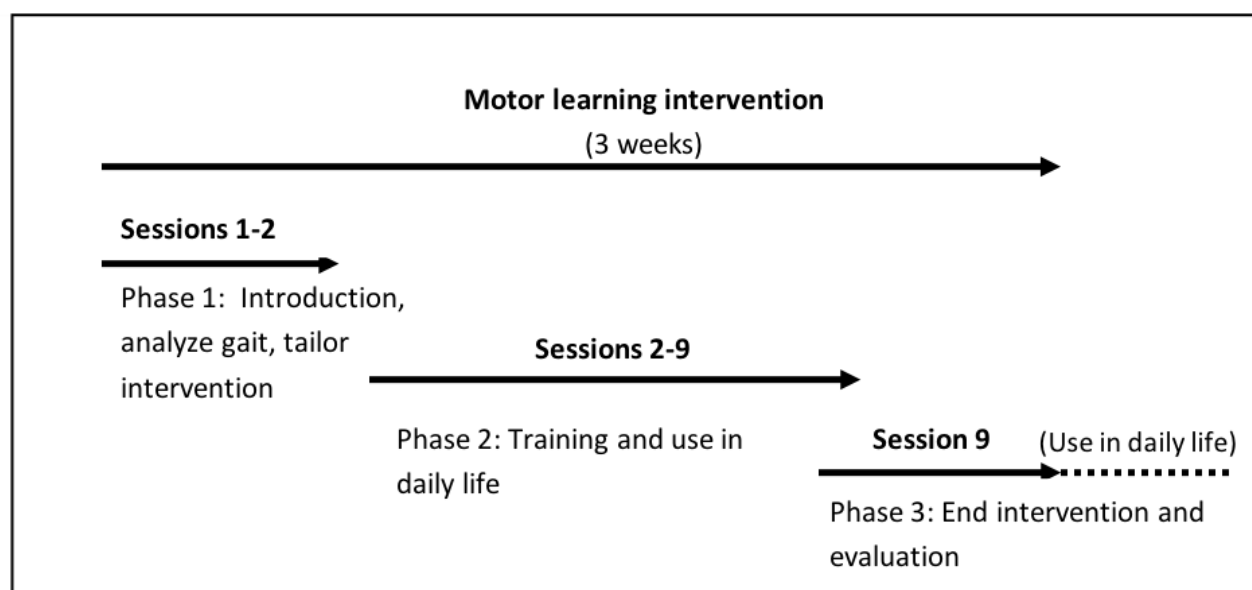
The chosen intervention period was based on a preliminary study of Kleynen et al [28] that demonstrated that 3 weeks was a feasible period to develop and practice analogies with people after stroke. All participants will receive 9 training sessions in a 3-week intervention period, that is, 3 training sessions per week (Figure 2). Each training session takes place at the home

of the participants and lasts for 30 min. Participants were asked to use the instructions in daily life (unguided therapy) and after the 3-week intervention period. To standardize the training content as much as possible, the therapists involved in the study will be trained before the start of the study. During 5 standardization training sessions, the intervention guideline will be discussed, explicated, and the therapists will be trained with the help of example cases. During the trial, therapists will attend 3 evaluation sessions to discuss the progress of the study and possible cases or difficulties they may experience during the intervention.

Figure 1. Characteristics of the interventions.

Figure 2. Overview of the gait training sessions.

Implicit Condition

Within the implicit condition, the concept of analogy learning is the leading approach as it has shown to adopt characteristics of implicit motor learning [24,27,28] and provides therapists with a practical and feasible guideline to organize gait training. To choose and develop appropriate analogies, the same procedure as used by Kleynen et al is followed [28]. A booklet with examples of possible analogies will be available for the therapists and patients as a source of inspiration. Preferably, analogies are developed based on the participants' experiences and background to promote the personalized and meaningful aspects of analogy learning [28]. All analogy instructions used in the trial will be documented. In addition to analogy learning, the therapists are allowed to use elements based on the characteristics of implicit motor learning as reported under the implicit column in Figure 1.

Explicit Condition

Within the explicit condition, gait training is organized by creating a learning environment that is (more) explicit in nature. Practice will be organized based on the characteristics of explicit motor learning as reported under the explicit condition in Figure 1. The condition is similar to the first (cognitive) stage of motor learning according to Fitts and Posner [34] that is characterized by the use of many explicit instructions, explaining precisely how motor skills should be performed. This stage is verbal and cognitive of nature. Contrary to the implicit condition, the explicit condition strives to maximize the number of explicit verbal instructions. The explicit instructions that have been used in the trial will be documented by the therapist's in treatment logs.

Measurements

All measures will be assessed by independent, blinded, and trained assessors at 3 assessment points (T0, T1, and T2; Table 1) and will take place at the participant's home. The primary outcome parameter is walking speed measured in meters per second using 10MWT. First, demographics are described, and then, the primary and secondary outcome measures are reported.

Demographics

At baseline, the following demographic and prognostic information is collected (T0): age, gender, time post stroke, affected side, walking aids, educational level, cognitive level (Montreal Cognitive Assessment, MoCA) [35], static balance and fall risk (Berg Balance Scale) [36], measures of mobility and disability (Rivermead Mobility Index) [37], and ability to make movements outside the synergetic patterns (Fugl-Meyer assessment of the lower limb) [38]. To assess the propensity for conscious motor processing, the Dutch version of Movement Specific Reinvestment Scale (MSRS) is used [39,40].

Walking Performance Measures

Walking performance is measured using the 10MWT [41] and the Dynamic Gait Index (DGI) [42]. To assess the robustness of the obtained performance, walking will also be assessed over a longer period (1-month follow-up) and under secondary task loading.

10-Meter Walking Test

Gain in walking speed has been associated with a transition to a higher class of ambulation, resulting in a better function and quality of life [41,43]. Next to statistical significance, the MCID will be used to assess clinical relevant differences. The MCID for walking speed in people after stroke has been established at the minimal difference of 0.16 m/s [33]. Exceeding this threshold indicates that the participants obtained a clinically meaningful improvement.

Table 1. Overview of measurements used in this study.

Data	Time	ICF[a] level
Demographics		
Age, gender, time post stroke, affected or nonaffected side, walking aids, educational level	T0	Personal factors
Montreal Cognitive Assessment	T0	Body functions and structure
Berg Balance Scale	T0	Activity level
Rivermead Mobility Index	T0	Activity level
Fugl-Meyer Assessment	T0	Body functions and structure
Walking performance		
10-meter walking test	T0, T1, T2	Activity level
Dynamic Gait Index	T0, T1, T2	Activity level
Dual task	T0, T1, T2	Activity level
General outcome measures		
Movement Specific Reinvestment Scale	T0, T1, T2	Personal factors
Verbal protocol	T2	N/A[b]
Stroke Specific Quality of Life Scale	T0, T2	Participation level
Global Perceived Effect scale	T2	N/A

[a]ICF: International Classification of Functioning, Disability, and Health.

[b]N/A: not applicable. The ICF level is not applicable for the Verbal Protocol and Global Perceived Effect Scale as these measures do not examine health or disability but evaluate the intervention.

Dynamic Gait Index

The DGI is a physical performance test that assesses the gait, balance, and fall risk and has shown to have a good reliability and validity in people after stroke [44,45]. Eight different tasks related to the balance and gait, for example, walking, turning, and stepping over objects are assessed [46]. The performance will be scored according to the modified DGI as proposed by Shumway and Cook as the extended scoring system has shown to possess good psychometric properties [42,47].

Dual Task

In this study, people will be asked to complete a tone-counting task similar to that proposed by Wilson et al [48]. In this task, people will be exposed to 4 different sounds (buzzer, ping, tone and bell ring) in a randomized order over a 30-s time period. They will be asked to only count a specific target sound (eg, bell ring) and ignore the other 3 distracting sounds. The task will be performed twice, once as a single task and once while walking concurrently (dual task). The actual number of tones will be compared with the estimate number of tones by the participants. Error scores (actual minus estimate) will be calculated as a measure for the dual-task performance.

Self-Reported Measures

Movement-Specific Reinvestment Scale Adapted for Gait

The MSRS is a questionnaire that measures a person's inclination for conscious control. People after stroke have shown to have greater propensity to conscious processing compared with the age-matched, nondisabled population [49,50]. In this study, an adapted version of the MSRS specific to gait is used. Adapted versions of the MSRS have been used before, for

example, for putting movements in golf [51,52]. The MSRS contains one factor related to conscious control (conscious motor processing) and one related to self-consciousness about movement (movement self-consciousness). Each factor of the MSRS comprises 5 statements, such as "I try to think about my movements when walking" (conscious motor processing) and "I am concerned about what people think about me when I am walking" (movement self-consciousness). The statements will be assessed with binary response (yes/no) [40]. The MSRS will be measured at baseline (T0) to describe the population and over time (T0, T1, and T2) to assess how much gait-related conscious processing takes place.

Verbal Protocol

To assess the amount of explicit knowledge, a verbal protocol questionnaire as used in Orrel et al will be administered after the 3-week intervention [22]. Explicit knowledge is assessed by examining the number of explicit rules that the participant uses during walking. Participants will be asked to report any "rules, methods, or techniques" that they have thought about or used and that have improved or impaired their walking performance. A rule is defined as any statement containing at least one of the following aspects: a movement or position of one limb, a movement or position of one joint, a velocity of a limb movement, an angle or direction of a joint or the spine, or the placement of the walking aid. Each statement containing a single limb, joint, or other body part will be counted as 1 rule. If a statement contains 2 (or more) different limbs, joint and body parts, or different directions or angles, they are counted separately (eg, "I tried to lift my foot and put it more forward."). Statements are excluded if they are irrelevant to walking performance or do not refer to technical aspects about walking

(eg, "More concentration needed."). The answer to the verbal protocol will be screened by 2 independent researchers who will be blind to the experimental condition. Their agreement will be investigated using a correlation coefficient (or ICC).

Stroke and Aphasia Quality of Life Scale

The *Stroke and Aphasia Quality of Life Scale (* SAQOL-39) is assessed at baseline and after the intervention to measure the health-related quality of life [53]. The questionnaire contains 39 items and is developed for people after stroke and is feasible to use for people with aphasia. The SAQOL-39 is a short version of the original SAQOL (53 items) and has shown to be an acceptable, reliable, and valid measure of the health-related quality of life [53].

Global Perceived Effect

The *Global Perceived Effect* scale is a reliable method to assess the participant's satisfaction and will be used to evaluate the participant's perception of the intervention [54]. The Global Perceived Effect scale will involve the following question: To which extent did your walking ability change over the last three weeks? The question will be scored on a 7-point Likert scale from "completely improved" to "completely deteriorated."

Process Evaluation

To gain an insight into the process-related factors that may have influenced the effectiveness of the 3-week analogy learning walking intervention, a process evaluation will take place along the study [55]. Data will be collected to (1) asses to what extent the therapists delivered the interventions as intended (fidelity), (2) explore the therapists' opinions and experiences about the interventions with regard to the feasibility and possible effects, and (3) explore the patients' opinions and experiences about the interventions with regard to the feasibility. Table 2 represents the data collection methods used to assess the different aspects of the process evaluation. For both groups, the provided instructions will be documented and evaluated in the therapists' logs. In addition, short questionnaires will be used to administer the therapists' and participants' opinions about the gait training after the completion of the 3-week intervention. To explore the extent to which the interventions were implicit or explicit in nature, the verbal protocol will be assessed. Evidence indicates that implicit learning is typically characterized by the less accumulation of explicit rules compared with explicit learning [24,56].

To monitor the integrity of the intervention, self-reported (subjective) and audio-recorded (objective) data will be evaluated. First, all therapists are required to self-report any

deviations from the treatment protocol or other incidents during the session in a log after every session. All instructions used during therapy sessions will be recorded in the therapists' and patients' logs. Furthermore, patients can use the log to write down any possible events that might have occurred during unguided therapy. The patient log is, therefore, only used as a reminder for unguided therapy and as a communication tool between therapists and participants. Second, 10 gait trainings will be randomly selected (5 implicit and 5 explicit interventions) and audio recorded. Both self-reported and audio-recorded data will be screened to evaluate whether the intervention was delivered according to the protocol.

Data Analyses

Baseline scores of demographic and prognostic data and primary and secondary outcome measures will be used to compare the 2 groups. Only data of the participants who attended minimum of 7 or more of the therapy sessions will be considered as adherent and processed in the statistical analysis. Statistical analysis will be conducted to determine significant differences between groups and over time (baseline and postintervention performance). A repeated measure analyses will be used to compare the 2 groups (implicit and explicit) at 3 different time points (before, after, and after 1-month follow-up). Post hoc tests with correction for multiple testing will be used to explore effects over time and between groups. Subgroup analysis will be performed on cognition (MoCA score <21) [35]. An alpha level of .05 will be set for all tests. The primary outcome measure, walking speed, will also be described with reference to clinically relevant differences between groups (MCID: 0.16 m/s) [33]. All datasets used or analyzed during this study are available from the corresponding author on a reasonable request.

Data will be analyzed according to an intention-to-treat and per-protocol principle. In the intention-to-treat, data of the participants are analyzed according to their original treatment allocation. If self-reported (subjective) and audio-recorded (objective) data reveal that cases are not delivered as intended, then the analyses will be performed using the per-protocol principle. Within this study, protocol deviations are defined as "deviations from the protocol that occur in two or more sessions." If protocol deviations were observed, then data from this person were not included in the per-protocol analysis. Data in the process evaluation related to the therapists' and patients' opinions and experiences toward the feasibility of the intervention and perceived benefits will be analyzed by means of descriptive statistics. Free comments and clarifying examples may be quoted and used to describe personal experiences of the therapists or participants.

Table 2. Measures for the process evaluation. A checkmark indicates with which measure the question is examined.

Questions	Measures			
	Therapist Log	Audio recordings	Therapist questionnaire	Patient questionnaire
To what extent did the therapists deliver the interventions as intended (fidelity)?	✓	✓	✓	
How did the therapist's experience delivering the interventions with regard to the feasibility and possible effects?			✓	
How did the patients' experience the intervention with regard to the feasibility?				✓

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Results

The entire project was funded in September 2015. Patient enrolment began in March 2017 and is expected to continue until July 2018. Following completion of data collection, data cleaning and analyses will take place. The first study results are expected to be submitted for publication in 2019.

Discussion

In this paper, we described the methodology of a randomized controlled single-blinded study that evaluates the potential effects of implicit motor learning compared with explicit motor learning in the gait rehabilitation of people suffering from stroke. The relevance of the study and the advantages and disadvantages of several aspects of the chosen design are discussed.

From Laboratory Setting to Clinical Practice

Although motor learning research is growing exponentially, most published studies have been performed in laboratory settings. However, it is important to understand the application of motor learning within clinically relevant environments and the influence of interventions on the completion of everyday functional tasks [18,57]. A recent systematic review on implicit motor learning in people after stroke pointed out that studies performed within clinical settings are limited [18]. Of the 20 included studies, only 1 study involved a clinically relevant task [22]. To improve the generalizability of research findings toward clinical practice and to the broader population, various choices on different aspects in the research design had to be made. First, with regard to the task and environment, this study involves gait training that takes place at the homes of the participants. Gait is a functional daily life motor skill, and it is advised to organize practice in a context-specific environment [4,58]. Therefore, compared with the current state of evidence, this study adds insights into the effects of motor learning in a clinically relevant environment and for a clinically relevant task.

Second, in this study, the motor learning conditions are tailored to the individual participants. Most implicit motor learning studies use strict research protocols in which each participant usually receives the exact same instructions (eg, the whole experimental group receives the same right-angled triangle analogy to learn topspin forehand in table tennis), whereas the explicit learning is promoted by using the same set of verbal instructions [24]. A one-size-fits-all approach may not be ideal for the clinical population as they generally demonstrate a large variety in degree and types of impairments. The use of personalized analogies allows the physiotherapists to respond to the individual walking impairments and emphasize on the meaningful component of analogy learning. With a personalized approach (more comparable with the real-life practice), the instructions may be less standardized. Therefore, steps were undertaken to ensure the quality of the interventions. Before the study, all therapists were familiarized and trained with the implicit and explicit conditions. Measures (therapists' logs and audio recordings of the interventions) were selected to evaluate whether the trainings were delivered as intended, and data will

be analyzed as per the intention-to-treat and per-protocol (see the Data Analyses section).

Methodological Aspects

Within this study, extra attention was given to the following 3 methodological aspects in designing the intervention: contrast, content of the interventions, and target population. First of all, it is important to address that in many rehabilitation studies, the contrast between the intervention and control group (generally usual care only) turns out to be too modest, which therefore results in neutral study results [59]. The underlying reason may be that rehabilitation interventions are often too complex to control for influences of other interventions and that the control intervention group (therapy as usual) is often poorly described. We tried to overcome these problems by including participants in the chronic phase of recovery, who do not receive additional interventions directed at the improvement of gait. Furthermore, we strive to ensure the contrast of the interventions by using a guideline, written protocol. In this protocol, the delivery of both conditions is clearly defined. It transparently describes how the 2 interventions differentiate from each other. To ensure the integrity of the intervention, the logs and audio-recorded therapy sessions will be conducted and evaluated.

Another decision we would like to address is the choice for the interventions. In clinical practice, often mixtures of implicit and explicit forms of learning are used or therapists switch between different forms of learning [15,60]. However, it remains unclear whether mixing implicit and explicit learning or switching between the forms is effective and/or necessary. The current design is necessary to evaluate the effects of implicit versus explicit learning in clinical practice, and so we believe that it is (ethically) legitimate to compare 2 distinct interventions and not use "therapy as usual" as a control intervention. The interventions in this study will be delivered in a personalized manner regarding overall components of the interventions, for example, the sort of gait impairments, amount of repetitions, and use of personalized analogies. However, the content of the interventions applied is clearly outlined in the guidelines, and therapists are required to strictly follow these.

Furthermore, within the target population, people experiencing cognitive impairments or communicative restrictions are often excluded. In this study, we strive to include a sample that reflects the broad range of impairments reported after stroke. In earlier studies, it has been shown that motor learning interventions might be effective, also for people with cognitive and/or communicative impairments [27,28].

Implicit Motor Learning

Scientific evidence describes that implicit learning is typically characterized by robust dual-task performance, durable performance over time, and less accumulation of explicit rules [24,56]. The dual-task measure and the 1-month follow-up session were specifically chosen with respect to these implicit characteristics. First, walking while concurrently carrying out a secondary (tone counting) task [48] places high information-processing demands on the learners. In contrast to explicit learners, implicit learners showed that performance was not disrupted in dual-task conditions, which indicates that they

may be able to free up attentional resources to perform the secondary task [24]. We therefore predict that the implicit condition will remain stable under secondary task burden. For this reason, implicit learning may be particularly beneficial for those who experience cognitive impairments that are commonly seen in people after stroke.

Then, a recent study by Tse et al [25] found performance improvements after a 2-day separation; however, they recommended to include a longer separation to test skill consolidation. This study will therefore evaluate performance after the 1-month follow-up period. It is hypothesized that performance improvements in the implicit group will remain robust over a longer period (1-month follow-up). To make statements about long-term effects within rehabilitation, it may be desirable for future studies to include even longer follow-up periods (>3 months). Finally, a verbal protocol will be assessed because it is hypothesized that participants within the implicit learning group will report fewer explicit rules than the control group, which would be in line with the findings of earlier studies [23,24]. Even though the starting point of the explicit intervention is to use many verbal explicit instructions and provide more details on the motor performance, the exact number of explicit rules will be tailored to the ability of the patient to process these rules. Therefore, in practice, some patients might receive higher numbers of explicit rules than others. Still, we hypothesize that the explicit group will require more explicit rules compared with the implicit group.

Conclusion and Implementation

With the description of the study design, we hope to contribute to the discussion on how a tailored but standardized form of implicit motor learning could be applied in clinical practice. The relevance of the study and the advantages and disadvantages of several aspects of the chosen design are discussed (eg, personalized approach, sample selection).

Authors' Contributions

LJ, MK, AB, and SB conceived and designed the study. LJ, MK, and SB wrote the first version of the manuscript. LJ, MK, KM, AB, and SB critically revised the manuscript for the relevant intellectual content. All authors read and approved the final version for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer review report by Dutch sponsor, Stichting Innovatie Alliantie (Innovation Alliance Foundation).

[PDF File (Adobe PDF File), 161KB - resprot_v7i5e142_app1.pdf]

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Abbreviations

10MWT: 10-meter walking test
DGI: Dynamic Gait Index
MCID: minimal clinically important difference
MSRS: Movement Specific Reinvestment Scale
SAQOL-39-NL: Stroke and Aphasia Quality Of Life

Protocol

Examining the Impact of Trauma-Informed Cognitive Behavioral Therapy on Perinatal Mental Health Outcomes Among Survivors of Intimate Partner Violence (The PATH Study): Protocol for a Feasibility Study

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Abstract

Background: Intimate partner violence (IPV) is a pervasive public health problem, impacting the health and quality of life of survivors worldwide. The trauma of IPV is associated with a high incidence of mental illness, namely depressive and anxiety disorders, and posttraumatic stress disorder (PTSD). Moreover, literature endorses cognitive behavioral therapy (CBT) interventions as a gold standard for those with symptomatology consistent with anxiety disorders, mood disorders, and PTSD. However, efficacy has not been evaluated among a population of pregnant survivors of IPV.

Objective: We present the protocol that will be used to explore the efficacy of trauma-informed cognitive behavioral therapy on maternal and child health outcomes for pregnant women with PTSD, depression, or anxiety symptomatology resulting from IPV. A secondary aim will be to test the validity and feasibility of study methodology to support the successful implementation of a full-scale randomized controlled trial.

Methods: The Promoting Attachment Through Healing (PATH) study will use a mixed-methods approach grounded in an intersectional feminist framework to explore the effectiveness of trauma-informed CBT for pregnant survivors of IPV. Study participants will be recruited through the hospital-based Perinatal Mental Health Clinic (London, Ontario, Canada). A feasibility sample of 20 pregnant women (cohort 1) will be selected to engage in an eight-session antenatal CBT intervention facilitated by the program's perinatal clinical nurse specialist, with evaluation at baseline, at two months postpartum (intervention and online questionnaire), and at six and twelve months postpartum (online questionnaire only). Concurrently, we will conduct a retrospective audit of 100 medical charts (cohort 2; 50 charts of perinatal women who received CBT and 50 charts of women who did not receive perinatal CBT) from the past five years. The efficacy of the intervention will be based on a reduction of mental illness symptomatology, improved maternal-infant attachment, maternal coping, and maternal quality of life. Additionally, the feasibility of the protocol and acceptability of the intervention from the women's perspective will be examined. Inductive content analysis of all qualitative data will be used to determine common themes. Additionally, descriptive statistics, including measures of central tendency and dispersion, will be computed for all continuous variables. Alternatively, frequency tables will be constructed for all categorical variables.

Results: The work reported here is in the proposal phase. Once the protocol is implemented, we will report the results in a follow-up paper. Participant recruitment for cohort 1 has started and we have finished data collection for cohort 2. It is anticipated that the results will be available by the end of 2018.

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Conclusions: Findings will assess the acceptability of the study methodology and protocol for a full-scale randomized controlled trial. Furthermore, if CBT is proven effective for pregnant survivors of IPV, this intervention could be readily adopted by health care and social support services, thereby contributing to an improved standard of care for this unique population.

Trial Registration: ClinicalTrials.gov NCT03536442; https://www.clinicaltrials.gov/ct2/show/NCT03536442 (Archived by WebCite at http://www.webcitation.org/6zeurv1ay)

Registered Report Identifier: RR1-10.2196/9820

Introduction

Background

Intimate partner violence (IPV)—a term that encompasses any act of physical, sexual, or emotional abuse within the context of coercive control by an intimate partner [1]—is a significant public health concern [2]. Intimate partner violence does not discriminate based on socioeconomic status, culture, or religion, and research indicates the global burden disproportionately impacts women [3], with gender-based violence deeply rooted in the patriarchal values espoused throughout history [4]. According to the most recent Statistics Canada profile on family violence, nearly 92,000 cases of IPV were reported to police in 2015, and of those, 79% of survivors were women [5]. While these numbers are deeply unsettling, it is perhaps more alarming that an estimated 1 in 4 Canadian women will be affected by IPV in their lifetime [6].

Ultimately, chronic victimization and coercive control [1] can have truly devastating consequences, including significant mental health challenges that follow survivors across the lifespan [7-9]. A recent meta-analysis and systematic review of 41 studies found women who had experienced IPV were considerably more likely to be diagnosed with a depressive disorder, anxiety disorder, or posttraumatic stress disorder (PTSD) [10]. Importantly, such disorders are more prevalent during pregnancy [10-12], with many studies suggesting the perinatal period poses an elevated risk of IPV [13,14].

Pregnancy is a time of significant physiological change [9]. Newly acquired fatigue, physical pain and discomfort, and emotional irregularity greatly impact one's ability to cope with environmental stressors and engage in health promotion behaviors [15-17]. When combined with the intimate and invasive nature of perinatal care, it is not surprising that this time period may be traumatic and potentially triggering (in relation to PTSD) for survivors of IPV [18,19]. This is especially salient for those with symptomatology of depression, anxiety or PTSD [7,11,20]. Additionally, the highly-medicalized nature of prenatal interventions, labor and delivery, and postpartum care further contributes to feelings of vulnerability and powerlessness, thereby compromising the mental health and wellbeing of at-risk women [21]. Collectively, these factors substantially increase the likelihood of obstetrical complications including infant prematurity, low birth weight, and developmental delays [22-24]. Furthermore, such trauma and poor mental health are known to negatively impact maternal-child attachment [25], which can significantly affect the development of the child over the course of their lifespan [26-28].

Despite the pervasive nature of IPV and its deleterious health and social sequelae, particularly affecting childbearing women, there remains a considerable dearth of nursing and allied health literature evaluating mental health interventions for this population [29]. There is a critical need for individualized, trauma-informed care to facilitate optimal maternal and child health outcomes across the lifespan [29,30]. Fortunately, viable treatment options, such as cognitive behavioral therapy (CBT) exist to address such challenges; however, research exploring the efficacy of CBT among pregnant populations is lacking. As such, the purpose of the aptly named Promoting Attachment Through Healing (PATH) study is to test the suitability of CBT for the treatment of IPV-related depression, anxiety, and/or PTSD among pregnant women, which can in turn foster meaningful maternal-infant attachment and improve overall health and well-being.

Objectives

The two overarching goals for this pilot study are: (a) to explore the efficacy of trauma-informed cognitive behavioral therapy (henceforth referred to as CBT) on maternal and child health and attachment outcomes for pregnant women with PTSD, depression, or anxiety symptomatology, resulting from IPV; and (b) to test the feasibility and acceptability of study methodology to support the successful implementation of a full-scale randomized controlled trial. To assess the ability of the proposed research to achieve the desired effect, we present five objectives:

1. To determine the impact of antenatal CBT on PTSD symptomatology among at-risk childbearing women
2. To determine the impact of antenatal CBT on depressive symptomatology among at-risk childbearing women
3. To determine the impact of antenatal CBT on anxiety symptomatology among at-risk childbearing women
4. To determine the impact of antenatal CBT on maternal-infant attachment among at-risk childbearing women
5. To determine the feasibility of the study protocol, by evaluating its process coherence, resource requirements, and perceived value through participant feedback

Methods

Design

This pilot project will consist of two cohorts: participants receiving CBT (cohort 1), as well as a retrospective chart audit of individuals who participated in the same CBT treatment within the last five years (cohort 2, intervention arm), and participants who received the accepted standard of care (cohort 2, standard care).

Cohort 1

A sample of 20 women currently attending the hospital-based, outpatient Perinatal Mental Health Clinic (London, Ontario, Canada) will be invited to participate in an eight-session antenatal CBT program facilitated by the clinic's perinatal clinical nurse specialist (PCNS). CBT is currently the gold-standard approach for treating depression and anxiety. What is unique about this intervention is that it is tailored to the antenatal period and integrates attachment theory. Typically, women undergo initial screening at their pre-admission appointment for signs and symptoms of depression, anxiety, and PTSD, as well as for history of IPV. If women meet any of these criteria, they are referred for in-hospital social work or psychiatry consultations as necessary. While this intervention is currently provided to a small subset of women receiving antenatal care at the clinic, its efficacy remains untested. As such, this is considered a "specialty service" provided to identified at-risk women, and is not considered the accepted standard of care at this time.

Cohort 2

A retrospective medical chart review of 100 women will be conducted. All women must have received antenatal care at the recruiting hospital within the last five years and screened positive for IPV. This time frame was selected as it is representative of the duration in which the clinic's current PCNS has been providing CBT to at-risk women. Of the 100 charts selected, 50 women must have participated in the CBT program (intervention arm), while the remaining 50 who did not will be assigned to the standard care group (these participants would have been eligible to participate but were not referred due to either lack of knowledge of the CBT program or a lack of support of the CBT program by the main health care provider). A sample size of 50 for both groups (intervention arm and standard care) will be sufficient to determine the feasibility of the study protocol for a future large-scale randomized control trial (RCT) [31].

Participant Inclusion Criteria

Cohort 1

Inclusion criteria include: 1) English-speaking; 2) pregnant women (any gestational age); 3) living in Ontario; 4) attending the Perinatal Mental Health Clinic at the recruiting hospital; 5) a history of IPV (disclosed to the PCNS during their intake assessment); and 6) symptomatology consistent with PTSD, depression, or anxiety that adheres to the diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V (as assessed by the PCNS at intake).

Cohort 2 (Intervention and Standard Care Arms)

The inclusion criteria above apply to the intervention arm of cohort 2 as well. Additional criteria include: 1) received PCNS-delivered CBT at the Perinatal Mental Health Clinic in the past five years; and 2) at least 50% of the data required for the chart data extraction is present.

For the standard care arm, additional criteria include: 1) having received antenatal care (but not PCNS-delivered CBT) at the Perinatal Mental Health Clinic in the past five years; and 2) at least 50% of the data required for the chart data extraction is present.

Recruitment

Cohort 1

Participant recruitment will be facilitated through the PCNS at the London Health Sciences Center (LHSC) in the Perinatal Mental Health Clinic. Women who are receiving antenatal care at the clinic and meet the above eligibility requirements will be provided with a business card, should they wish to learn more about the study. To mitigate any undue influence or pressure to partake in the pilot project, potential study participants will be informed that their involvement is voluntary, and their involvement with the study will have no impact on the nature or quality of care. Participants interested in the study will be asked to contact the research team, at which time the safety protocol will be enacted, and eligibility and recruitment will be completed.

Cohort 2 (Intervention and Standard Care Arms)

Recruitment will be facilitated through the health records department at LHSC. The PCNS will identify participants who have received PCNS-delivered CBT in the last five years (intervention arm) and a general chart audit from the same time period will be used for the standard care arm. For both samples, a random sample approach will be undertaken wherein the research assistant (RA) uses a table of random numbers to select charts.

Safety and Security

Ensuring the physical and emotional safety of women participating in the study is of paramount importance. Upon enrollment in the study, a safety plan will be enacted, outlining secure methods of communication (via email and telephone), information storage, and an emergency protocol if contact with the participant is lost unexpectedly. This particular safety plan has been utilized successfully by both principal investigators in previous research involving survivors of IPV without any adverse events [32]. To further mitigate the risk that perpetrators of violence will discover their partner's involvement in the study, strict privacy and confidentiality precautions will be adhered to during the transfer and storage of participants' health information and demographic data. All personal identifiers will be removed and replaced with an encrypted identification code unique to each participant, thus ensuring anonymity. Electronic documents will be stored on the university server behind a secure firewall, while physical copies of interview transcripts and questionnaires will be stored on campus within locked research offices.

Given the sensitive and potentially triggering nature of content raised during structured in-person interviews, all study personnel will be trained to identify acute signs of distress and initiate a stress reaction protocol. This will involve the immediate discontinuation of the interview, followed by referrals to appropriate crisis stabilization and treatment interventions if needed, including the 24-hour helpline for abused women. All participants will be offered a handout describing the signs and symptoms of stress reaction along with various community resources capable of providing comprehensive mental health support.

Finally, should a participant disclose suicidal ideation—whether shared with the PCNS or RA directly, or flagged as high risk (indicated by an affirmative response to questions of self-harm) when completing the Edinburgh Postnatal Depression Scale (EPDS)—they will be immediately referred to the London-Middlesex Suicide Prevention Council Support Line by the individual, or through automatic prompt via the online questionnaire. If it is suspected that juvenile dependents of study participants are experiencing abuse or neglect, members of the research team will report the need for protection to the Children's Aid Society, as per regulation set forth by the Child and Family Services Act (1990).

Data Collection

Data collection will occur simultaneously for both cohorts.

Cohort 1

Data collection will occur at baseline (T1; prior to the PCNS-delivered CBT and during pregnancy), two (T2), six (T3), and twelve (T4) months postpartum. At T1 and T2, a mixed-method data collection model will be utilized wherein women will complete a semistructured interview for approximately one hour (audio-recorded) and complete a short demographic survey. At T3 and T4, participants will be sent an electronic link to complete a questionnaire (or alternatively, if this is thought to be unsafe, a member of the research team will meet with the participant to complete a hardcopy version).

During the T1 data collection interaction, the study protocol will be thoroughly described and consent to participate will be obtained. Throughout the data collection period (T1-T4), a detailed safety plan will be reviewed (updated as needed), and participants will be provided a $25 honorarium (retail gift card) in recognition of their contribution to the study. To further reduce potential barriers to involvement, those in need of reimbursement for childcare or transportation expenses to attend the in-person interviews will be offered $15 and $10, respectively.

Cohort 2

A data abstraction instrument (developed by the co-principal investigators) will be used to collect data. Data will be pulled from multiple sources including: the e-chart, nursing chart, paper chart, and nursing care plan. Maternal data extraction will include: a) scope of mental illness, including diagnosis and current treatments; b) general physical and mental health status; c) obstetrical history; d) birth summary; e) care plan, including CBT interventions; f) evidence of learned CBT strategies or alternative coping strategies used during birth; g) birth experience; h) evidence of maternal-infant attachment; and i) demographics. Conversely, data extraction for infants at the time of parturition will include: a) gestational age; b) weight; c) length; d) head circumference; e) complications and interventions; f) Appearance, Pulse, Grimace, Activity, and Respiration (Apgar) score; and g) newborn physical exam. The chart review will take place at the recruiting hospital and does not require any patient contact. No identifying information will be collected, as the audit will be conducted for each chart in its entirety during a single data extraction period, thereby eliminating the need to refer back to any particular patient's chart.

Outcome Measures

All interviews and questionnaires seek to understand the lived experience of IPV within the context of pregnancy and childbirth, as well as the impact of CBT on the five primary study objectives described previously. Specifically, it is expected that this study will ascertain the impact of CBT on a) maternal mental health, and b) maternal-infant attachment. These outcomes will be measured using the PTSD Checklist (PCL-5), EPDS, Spielberger State-Trait Anxiety Inventory (STAI), World Health Organization Quality of Life Brief Assessment (WHOQOL-BREF), Maternal Attachment Inventory (MAI) and Proactive Coping Inventory (PCI). Each will be discussed in turn.

PTSD Checklist (PCL-5)

The PCL-5 is a PTSD Checklist for DSM-V symptomatology consisting of 20 items in a standardized self-report measure that assesses the presence and severity of PTSD [33]. Respondents indicate how much they have been bothered by a particular symptom over the past month using a 5-point Likert scale, with responses varying between 0 (not at all) and 4 (extremely). A total symptom severity score—ranging from 0 to 80—is obtained by summing the self-reported ratings for all 20 items, with higher scores indicating greater PTSD symptomatology. Based upon thorough psychometric evaluation [33], the PCL-5 has demonstrated excellent internal consistency (alpha=.94) and construct validity.

Edinburgh Postnatal Depression Scale

Postpartum depression will be measured using the EPDS—a 10-item screening questionnaire used to identify symptoms of a depressive disorder, as outlined in the DSM-5 [34]. Women are asked to answer each question by selecting the response that best describes their feelings during the previous 7 days. Responses are assigned points from 0 to 4, with higher values corresponding to more severe depressive symptomatology. Points from each question are summed, with total scores ranging from 0 to 30. The EPDS has been used consistently among perinatal practitioners since its inception, and is widely recognized as a valid and reliable screening tool with strong internal consistency (alpha=.83-.87) [35]. The EPDS has a cut score of 15 or more for antenatal women indicating a major depressive episode.

Spielberger State-Trait Anxiety Inventory

Anxiety among at-risk women will be assessed using the STAI [36]. The STAI is an introspective psychological instrument consisting of 40 self-reported items, separated into two subscales (ie, A-State and A-Trait), each with 20 items. "State anxiety" is defined as a transient momentary emotional status that results from situational stress, while "trait anxiety" represents a predisposition to react with anxiety in stressful situations [37]. All items are scored using a 4-point Likert scale (1-4), with totals ranging from 20 to 80 for each subscale, with higher scores suggestive of greater anxiety. Considerable evidence [36] attests to the construct and concurrent validity of the STAI (alpha=.86-.91).

World Health Organization Quality of Life Brief Assessment

Maternal quality of life (QOL) will be assessed using the WHOQOL-BREF, an instrument comprised of 26 items measuring the following four domains: physical health, psychological health, social relationships, and environment. Responses for each question range from 1 to 5 along a Likert-type scale, with higher scores corresponding to a greater self-perceived QOL. The WHOQOL-BREF has been found to have strong discriminant validity (r>.45) and internal consistency (alpha=.84) [38].

Maternal Attachment Inventory

Maternal-infant attachment will be evaluated using the MAI [39]. The MAI is a 26-item self-report instrument is measured on a four-point Likert scale, ranging from a) almost always, b) often, c) sometimes, and d) almost never. A total score is obtained by converting subjects' responses to corresponding numeric values as follows: a) 4 points, b) 3 points, c) 2 points, and d) 1 point. All items are summed, resulting in scores ranging from 26 to 104. Higher scores indicate stronger feelings of attachment toward the newborn child. This instrument was initially tested in a sample of 196 women at one month postpartum, resulting in acceptable internal consistency and validity (alpha=.85) [39].

Proactive Coping Inventory

Maternal coping will be measured using the PCI [40], a multi-dimensional coping scale that assesses how well individuals utilize resources in the development of positive coping strategies to combat distress. The PCI is comprised of seven subscales, each of which assesses a unique dimension: proactive coping, preventive coping, reflective coping, strategic planning, instrumental support seeking, emotional support seeking, and avoidance coping. All items are assessed on a 4-point Likert scale, ranging from 1 (not at all true) to 4 (completely true). Responses are summed to obtain a total score for each subscale, with higher scores reflective of greater proactive coping skills. All subscales were found to have good validity and high internal consistency (alpha=.71-.85) [40].

Feasibility

Feasibility of the intervention and protocol will be evaluated through the semistructured interviews with women in cohort 1. To ascertain feasibility, open-ended questions will be asked to evaluate fidelity and resource requirements. Fidelity will be assessed by examining the five core components of the intervention with global open-ended questions for each, such as:

1. What have you learned about the brain (and the brain during pregnancy)?
2. What have you learned about the nature of trauma and its effect on the brain?
3. What have you learned about the effects trauma can have on your attachment with your baby?
4. What have you learned about triggers?
5. What tools have you learned about to manage triggers?

Resource requirements will be assessed from: 1) a provider perspective by tracking the length of the CBT sessions and the number of sessions; 2) a patient perspective by tracking any costs incurred to participate in the CBT session (eg, travel, childcare, etc); and 3) a system perspective by tracking the use of facilities and referrals to other resources.

Acceptability

To assess acceptability of the intervention, we will ask four global open-ended questions assessing the perceived value of the intervention including:

1. What strategies do you see yourself using during labor/delivery and beyond?
2. How has your CBT work impacted how you feel about labor/delivery and beyond?
3. How has your CBT work impacted the way you feel towards your unborn child? Yourself? As a woman?
4. Would you recommend this intervention to someone else in a similar situation as you? Why or why not?

Statistical Analysis

For quantitative data, the overall impact of the PCNS-facilitated CBT intervention will be assessed using generalized estimating equations [41] to determine the effectiveness over time, and in contrast to standard care. Descriptive statistics, including measures of central tendency and dispersion, will be computed for all continuous variables and frequency tables will be constructed for all categorical variables.

Qualitative Analysis

For qualitative data using NVivo Software, an inductive content analysis will be executed to determine common themes [42]. This methodology supports a holistic and rich description of data, ideally suited to address project goals. This analysis will be grounded in an intersectional feminist framework [43]. This framework emphasizes that gender-based violence needs to be understood within the context of how identity and social location intersect and interact and how systems of power, oppression, and privilege shape women's lives [44,45]. Analysis will take place at the end of data collection and will be conducted independently and simultaneously by 2 investigators and a research assistant. NVivo software will support analysis through coding and providing a comprehensive data management system. Each coder will become immersed in the data and once saturation is reached coding will commence [46]. Initially, open coding data line by line will be used and when themes emerge

they will be organized into similar topics and then categories. Each category will be examined to determine meaning and will be assigned a working name and flexible definition. Axial coding will then be completed by recontextualizing the data that was coded into each category to determine consistency within the category (to decrease human bias in selective coding). Lastly, the categories will be re-examined to finalize the name and definition as well as to ascertain the underlying meaning of the theme within the context of the findings. Once each coder is finished coding, findings will be compared to ascertain if there is agreement on major emergent themes. If there is no agreement, a majority will be used to classify major themes.

Power

Cohort 1

A sample of 20 women was selected as this is a feasibility study and it is anticipated we will reach saturation (assessed by the sole interviewer with the use of field notes) in the qualitative data [46]. This sample will be used to inform future power analysis for the large-scale RCT.

Cohort 2

One hundred charts will be audited (50 from each of the two arms, the intervention and standard care arms). This sample size, for this feasibility study, was selected as it will allow us to extend the breadth and depth of analysis from cohort 1. This ultimately enhances the validity of the study's findings [31] by contextualizing the differences between the intervention and standard care, therefore contributing to valuable knowledge translation.

Results

The work reported here is in the proposal phase. Once the protocol is implemented, we will report the results in a follow-up paper. However, we hypothesis that PCNS-delivered CBT will result in decreased PTSD, anxiety, and/or depression symptomatology, and improved maternal-infant attachment, coping, and QOL. We also hypothesize this study will be feasible in terms of fidelity and deliverability, as well as be highly acceptable to participants.

Discussion

Study Rationale and Future Direction

We hypothesize that PCNS-delivered CBT will be effective in treating PTSD symptomatology, depression and anxiety disorders affecting the sample of pregnant women selected [47], thereby contributing to participants' improved QOL and maternal-infant attachment, and positive child health outcomes following birth.

The PATH study serves to build upon existing health literature that explores the positive impact of CBT for survivors of IPV and those experiencing mental health challenges [48-50] within periods of transformational change associated with pregnancy, childbirth, and motherhood. This feasibility study will help to address a current lack of literature in the area by filling a gap in intervention research aimed at improving the health and QOL of perinatal women who have experienced IPV and have symptomology consistent with PTSD, depression and/or anxiety.

Furthermore, successful implementation will help to determine the feasibility and acceptability of the study methodology and protocol, to support the future full-scale RCT. Efficacy will be determined in relation to a reduction in PTSD, anxiety, and depressive symptoms, and improvement in maternal-infant attachment, maternal coping, and maternal QOL. Feasibility will be assessed in relation to fidelity and resource allocation (from the provider, participant, and system perspectives) and acceptability will be measured in terms of perceived value from the participants' perspective.

Limitations

The proposed study is not without limitations, namely the small sample size, limited recruiting methodology, and high reliance on the PCNS who is delivering CBT at the recruitment site. The small sample size chosen for this feasibility study is a limiting factor for statistical analyses as well. The fact that recruiting is limited to a single site could also be problematic as this significantly decreases the pool of potential participants. Finally, the high reliance on the PCNS who is delivering CBT at the recruitment site also limits the pool of participants, in addition to potential concerns regarding scale-up and reproducibility of the intervention. While having one intervention decreases the variability in terms of consistent delivery of the intervention, it speaks to a potential difficulty in ascertaining if the results were due to the intervention alone or the intervention/interventionist.

Conclusions

This is the first intervention research of its kind examining the impact of perinatal CBT for women who have experienced IPV with mental illness. If the hypotheses of this research are correct, then not only would that support the scale-up of the intervention, it could also have far-reaching implications for individuals and society. Specifically, the findings would not only benefit individual participants and their families in terms of strengthened maternal-infant bonds and family units, but may also result in broader societal benefits, including reduced chronic health care utilization and associated treatment costs, as well as increased productivity, participation, and economic contribution within the London community [51,52].

Authors' Contributions

KTJ and TM conceptualized the study design and the writing of the manuscript. SP conceptualized the perinatal CBT intervention and participated in the development of the study design. BJ participated in the development of the manuscript and literature review. All authors approved this manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report.

[PDF File (Adobe PDF File), 96KB - resprot_v7i5e134_app1.pdf]

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Abbreviations

Apgar score: Appearance, Pulse, Grimace, Activity, and Respiration score
CBT: cognitive behavioral therapy
DSM-V: Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition
EPDS: Edinburgh Postnatal Depression Scale
IPV: intimate partner violence
LHSC: London Health Sciences Centre
MAI: Maternal Attachment Inventory
PATH: Promoting Attachment Through Healing
PCI: Proactive Coping Inventory
PCL-5: PTSD Checklist for DSM-5
PCNS: perinatal clinical nurse specialist
PTSD: posttraumatic stress disorder
QOL: quality of life
RA: research assistant
RCT: randomized control trial
STAI: State-Trait Anxiety Inventory
WHOQOL-BREF: World Health Organization Quality of Life Brief Assessment

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Protocol

Evaluating a Serious Gaming Electronic Medication Administration Record System Among Nursing Students: Protocol for a Pragmatic Randomized Controlled Trial

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Abstract

Background: Although electronic medication administration record systems have been implemented in settings where nurses work, nursing students commonly lack robust learning opportunities to practice the skills and workflow of digitalized medication administration during their formative education. As a result, nursing students' performance in administering medication facilitated by technology is often poor. Serious gaming has been recommended as a possible intervention to improve nursing students' performance with electronic medication administration in nursing education.

Objective: The objectives of this study are to examine whether the use of a gamified electronic medication administration simulator (1) improves nursing students' attention to medication administration safety within simulated practice, (2) increases student self-efficacy and knowledge of the medication administration process, and (3) improves motivational and cognitive processing attributes related to student learning in a technology-enabled environment.

Methods: This study comprised the development of a gamified electronic medication administration record simulator and its evaluation in 2 phases. Phase 1 consists of a prospective, pragmatic randomized controlled trial with second-year baccalaureate nursing students at a Canadian university. Phase 2 consists of qualitative focus group interviews with a cross-section of nursing student participants.

Results: The gamified medication administration simulator has been developed, and data collection is currently under way.

Conclusions: If the gamified electronic medication administration simulator is found to be effective, it could be used to support other health professional simulated education and scaled more widely in nursing education programs.

Trial Registration: ClinicalTrials.gov NCT03219151; https://clinicaltrials.gov/show/NCT03219151 (Archived by WebCite at http://www.webcitation.org/6yjBROoDt)

Registered Report Identifier: RR1-10.2196/9601

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KEYWORDS

video games; high fidelity simulation training; nursing education; medication errors

Introduction

Background

Ensuring clinician sciences students have access to appropriate and pedagogically robust clinical learning opportunities is important to generate future cohorts of competent practitioners. The wide-scale adoption of high-fidelity patient simulation tools into clinical education (ie, nursing, medicine, and pharmacy) [1,2] is increasingly being extended and amplified through the use of technology-enabled (ie, online) serious gaming and other gamified approaches [3,4]. Serious gaming or gamification has been defined by Koch et al [5] as "the use of game design elements in nongame contexts" for the purposes of engaging learners in solving complex problems. In nursing education, there is currently minimal use of immersive, technology-enabled, or gamified approaches for students to practice clinical skills and judgment [6,7]. Commonly, in-person, simulated practice with high-fidelity patient simulation provides students the only functional opportunity to learn various clinical skills (eg, medication administration) before interacting with real patients in health care environments such as hospitals and in the community [7]. Although this type of in-person simulation has been found to be extremely effective toward generating clinical competency and skills [8,9], virtually all this kind of learning is contingent on the availability of, and access to, a physical simulation laboratory. Given the increasing enrollment sizes and current financial restraints present in many universities and colleges, scalable, cost-effective, and authentic [10] technology-enabled approaches (including gamification) for clinical nursing education are warranted.

Electronic Medication Administration and Nursing Education

Electronic medication administration record (eMAR) systems have become more popular in many health care environments over the last decade, as a mechanism to improve medication safety. In brief, an eMAR system is a type of clinical technology that a health care provider (ie, nurse) uses to both validate and record the administration of medications. eMAR systems commonly use barcode technology to ensure that the correct medication is being administered to the correct patient at the correct time, dosage, and route [11]. Nurses are currently one of the largest user groups of eMAR technology [12,13]; therefore, it is essential that eMAR medication administration skills-building is fully embedded within nursing education. In clinical practice settings where eMAR systems are used effectively, statistically significant reductions in medication errors in comparison with those using paper-based medication administration processes have been reported [14]. Due to ongoing high rates of adverse medication events in both Canada and the United States [15,16], clinical technology such as eMARs may be essential for the reduction of medication-related errors [17,18].

One significant issue within nursing clinical education is competency and self-efficacy development in safe medication administration practices. Commonly, nursing students receive theoretical courses related to pharmacology and also clinically focused courses during the early years of their undergraduate education. Before students administering medications to real patients, learners usually participate in simulated, in-person learning opportunities within a laboratory setting. In these controlled learning environments, students can practice skills and further integrate their theoretical knowledge of pharmacology with professional practice skills related to medication administration. With recent advances in clinical technology such as eMAR systems [19], the complexity of the medication administration process has become a recognized nursing education and simulation issue [11,20-22]. Past research examining eMAR in nursing education simulation has outlined a range of factors limiting student success in this new modality of medication administration—namely, the amount of time and access students have to learn the unique workflows and clinical decision-making requirements in a digitized medication administration process [22]. There has been little research into whether serious gaming or gamification might be used as a tool to educate students in the complex tasks and processes inherent in medication administration [3,23], outside of the simulation laboratory. Finally, there are no known studies that examine whether medication administration gaming, in advance of simulated clinical practice, results in better nursing student learning, self-efficacy, and performance outcomes.

Objectives of the Study

The main objectives of this study are to examine whether the use of an eMAR simulation serious game (1) improves nursing students' attention to medication administration safety within simulated practice, (2) increases student self-efficacy and knowledge of the medication administration process, and (3) improves motivational (ie, attention, relevance, confidence, and satisfaction) and cognitive processing attributes (ie, invested mental effort and difficulty to learn game) related to student learning in a technology-enabled environment. Three specific research questions will be addressed in this study:

1. Does the use of an eMAR simulation game improve the eMAR medication administration safety for nursing students during in-person, simulated clinical practice?
2. Does the use of an eMAR simulation game improve learner self-efficacy and knowledge toward eMAR medication administration processes in nursing students for in-person, simulated clinical practice?
3. Does the use of an eMAR simulation game improve the motivational and cognitive processing attributes of nursing students regarding their learning of eMAR medication administration in a technology-enabled environment?

Methods

Development of a Prototype Electronic Medication Administration Record Simulation Game

At a large Canadian university in southern Ontario, a simulated eMAR system named the *SMART eMAR* was designed, developed, and implemented by faculty and students [24,25]. The SMART eMAR is used within the university's clinical simulation laboratory (CSL) and provides students the opportunity to practice medication administration processes during various in-person, simulated clinical practicum courses. The SMART eMAR is a cost-effective, scalable, and customizable platform that resembles a real clinical eMAR system in terms of both interface and usability. The system contains all the major decision support elements and functionalities of a real eMAR system, including color-coded decision support related to incorrect barcode scans of medication or patient identification bracelets, barcode scanning capabilities of a host of inert medications used in the CSL, auto-populating data fields for time stamps and date, and qualitative text fields for nurse signatures or commenting. Both the hardware and software components of the SMART eMAR are mounted onto hospital-grade Ergotron mobile carts to replicate the usability and physical appearance of a clinical workstation on wheels.

First, although the SMART eMAR was designed to have a simplistic eMAR user interface (vs eMAR platforms found in acute care hospital environments), students had a difficult time learning how to effectively use and administer medications using this system [11]. Findings from this previous research also suggested that nursing students did not feel that they possessed enough knowledge regarding the process of electronic medication administration or the clinical judgment factors (ie, specific time-dose dependencies associated with some medications) to effectively use the SMART eMAR in simulated practice [11,20]. Second, students reported that they did not feel they had adequate time with the SMART eMAR to fully understand the work processes required to use the system confidently [11]. These findings are consistent with other research examining medication administration by nursing students [26]. Gamification of the eMAR process was selected by the research team to be both an innovative and logical solution to address the learning barriers currently faced by students [11].

To assist with game development of an eMAR simulation game, the research team partnered with a video game company (Mikutech, Joydrop Ltd, London, Canada) that has significant experience in the areas of video game and software development, including the specialized fields of education, engineering, and health care [27]. Drawing on previous research and medication administration workflow on the SMART eMAR [11,24], 2 main teaching-learning directions were targeted in the eMAR simulation game development. First, the main objective of the eMAR simulation game was to afford students a virtual and immersive opportunity to practice medication administration using an eMAR system in a structured environment that provides feedback consistent with previously published best practices [11,20,25]. Second, the simulation game was planned to gamify the medication administration process for a range of patient's clinical presentations, with multiple feedback loops for each decision point along the medication administration pathway. Using a finite-state machine logic, each of these feedback loops could result in either *success, qualified success,* or *failure* in the administration process, which would be reported back to the student upon their completion of the medication administration event. As medication errors are commonly generated through a range of dynamic procedural, clinical decision-making, and human and environmental factors [28], the game was designed to be as expansive as possible for students to generate eMAR-enabled errors of all complexions, including incorrect medication dosage interpretation, administration timing, clinical indication and appropriateness, and other best practice processes deviations (eg, failure to wash hands before administration, failing to barcode scan the patient identification band or medication barcode, and failing to complete a vital signs assessment before administering an antihypertensive medication). If a student failed to attend to a specific medication administration best practice and further dependent on the severity of the error, feedback would be provided to the student on completion of the scenario, informing them of the number of errors made and brief rationale related to the mechanism of the error(s) themselves. Figure 1 provides a screenshot of an element of the game user interface, along with various manipulable objects that can spawn specific information (ie, drop-down menu to select a specific patient medication error, vital signs machine, patient dialogue, handwashing, scanning of barcodes, etc) related to the patient scenario and the medication administration context.

Study Design

The primary study design (phase 1) will consist of a prospective, 2-armed pragmatic randomized controlled trial. Phase 2 will consist of qualitative focus group interviews, conducted after the completion of phase 1.

Setting and Recruitment of Participants

Two waves of second-year baccalaureate nursing student participants will be contacted and recruited for participation in this proposed study at the beginning of 2 separate academic semesters: wave 1 will commence in September 2017 (fall semester) and wave 2 in January 2018 (winter semester). Due to the size of the second-year nursing student cohort (N=150) and resource limitations of the CSL, only half (n=75) of the students will partake in simulated clinical education in the CSL, per semester (split between fall and winter). Inclusion criteria for this study will be (1) second-year nursing students and (2) partaking in clinical simulated education either in fall 2017 or winter 2018 semesters. Students recruited in this study will not have had previous exposure to medication administration, and this simulated clinical experience will be their first formative interaction with medication administration and the SMART eMAR.

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Figure 1. Screenshot of the electronic medication administration record (eMAR) simulation game's user interface and various player-manipulable objects.
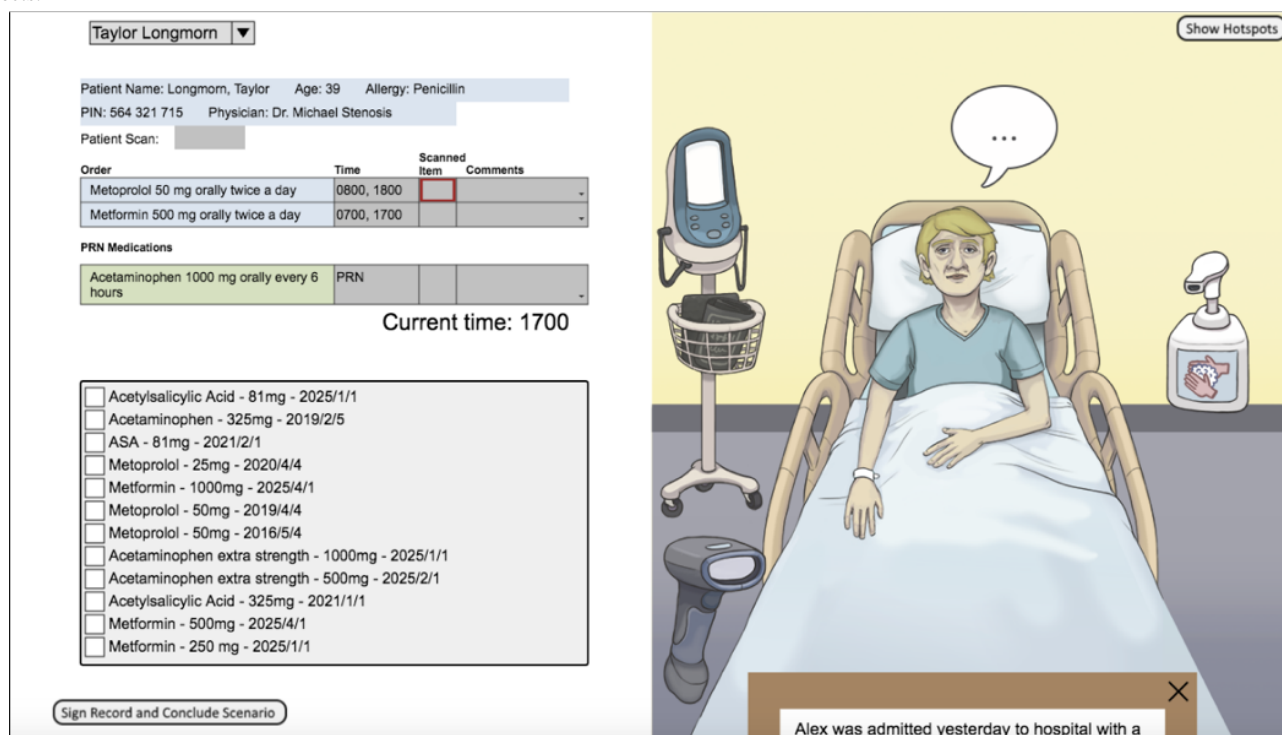
Before the start of each term, a researcher-led presentation will be delivered outlining the proposed study purpose, methods, and study benefits. Given the typical student enrollment within second year of the BScN program, it is expected that approximately 150 students will fit this inclusion criterion and be eligible for recruitment into the study. Participants will be offered a Can $5 gift card for a coffee shop as a nominal incentive to participate in the study. Due to the high recruitment success rate experienced in the corresponding pilot study completed in April 2016 (25/27, 93% of students sampled) [11], we estimate 120 participants will be recruited. By including at least 120 participants, phase 1 of our study will be able to detect an intervention effect size of 0.25, with a power of 0.8 and a .05 level of significance, based on a 2-tailed *t* test analysis, as calculated by G*Power 3.1 (Heinrich-Heine-Universität Düsseldorf, Germany).

Data Collection

Phase 1

After recruitment and enrollment into the study (week 1), nursing students in each semester will be randomized into either the intervention or control group and will be assigned a unique participant code number. The allocation ratio will be 1:1 (intervention or control group), following a simple randomization procedure (Microsoft Excel [Microsoft Corp.] random number table). Research team members involved in data collection will be blinded to the allocation; participants will become aware of their randomization on receipt of an email from the researchers outlining their allocation into the intervention or control group. At this time, students in the intervention group will receive access to the eMAR simulation game approximately 2 weeks in advance of their in-person simulation sessions with the eMAR technology in the CSL.

Along with access to the eMAR simulation game, students in the intervention group will also have access to other usual preparatory educational resources related to medication administration, such as a video demonstrating proper administration technique and a PowerPoint presentation on eMAR medication administration. To ensure a consistent duration of game intervention, students will be requested to use the eMAR simulation game for a minimum of 60 min (with no maximum) [29] before conducting their return demonstration of a medication administration using the actual SMART eMAR system in the CSL (starting week 5); analytics software operating in the background of the game will be used to track the average game play duration of participants. Students allocated to the control group will receive the usual preparatory resources related to eMAR medication administration, without access to the eMAR simulation game. At the conclusion of the trial in late October and February (week 9), all participants in the control group will receive access to the eMAR simulation game.

The duration of the active trial in each academic semester will be approximately 4 weeks, running the months of October and February. The simulated return-demonstration patient scenario that all students will be required to complete involves conducting a baseline physical assessment on a high-fidelity human mannequin simulator, performing the ordered medication administration using the SMART eMAR system, and conducting a patient follow-up assessment and documentation of the encounter in the patient's clinical record. All participants in the intervention and control groups will receive the same patient and medication administration scenario to maximize contextual internal validity.

Prepost data related to medication self-efficacy and knowledge will be collected through a Qualtrics (Qualtrics Inc.) Web-based

survey platform before (week 4) and after the simulated return-demonstration patient scenario (week 8). Cross-sectional survey data will be collected from the intervention group only, immediately after the simulated return-demonstration patient scenario (week 8; Figure 2).

Outcomes

Data will be collected by 4 data collectors (nursing graduate students with clinical backgrounds using eMAR technology) who will observe nursing student participants during their return demonstration of medication administration using the SMART eMAR (weeks 5-8). These data collectors will be trained by members of the research team before the study initiation to ensure the appropriate and consistent use of the checklist to collect participant data. Mock student return demonstrations and related data collection will be conducted to improve interrater reliability; Fleiss kappa coefficients will be calculated and used to further refine interrater reliability of the data collection procedure. A formalized checklist that has been developed and used previously in an adapted form by the research team [20] will be implemented as the primary data collection instrument for phase 1. This data collection checklist

will capture the following quantitative data during each participant's medication administration return demonstration using the SMART eMAR: (1) frequency of deviations from medication administration best practices, (2) number of actual medication errors or near misses generated by the student that violate the various medication best practices and provincial regulatory requirements related to medication administration [30,31], and (3) overall duration of time required by the student to complete the entire medication administration simulated scenario. Secondary outcomes using prepost survey data related to medication self-efficacy and knowledge will be collected using questions modified from previously developed and tested instruments [32,33]. Secondary outcome cross-sectional data will also be collected using questions modified from the Huang et al's [34] validated instrument that measures motivational (ie, attention, relevance, confidence, satisfaction) and cognitive processing of learning in game-based environments (20 questions, Cronbach alpha=.91). Measurement of motivational and cognitive processes of learning will identify levels of participant motivation related to cognitive load requirements demanded by the eMAR simulation game.

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram for electronic medication administration record (eMAR) game pragmatic trial.
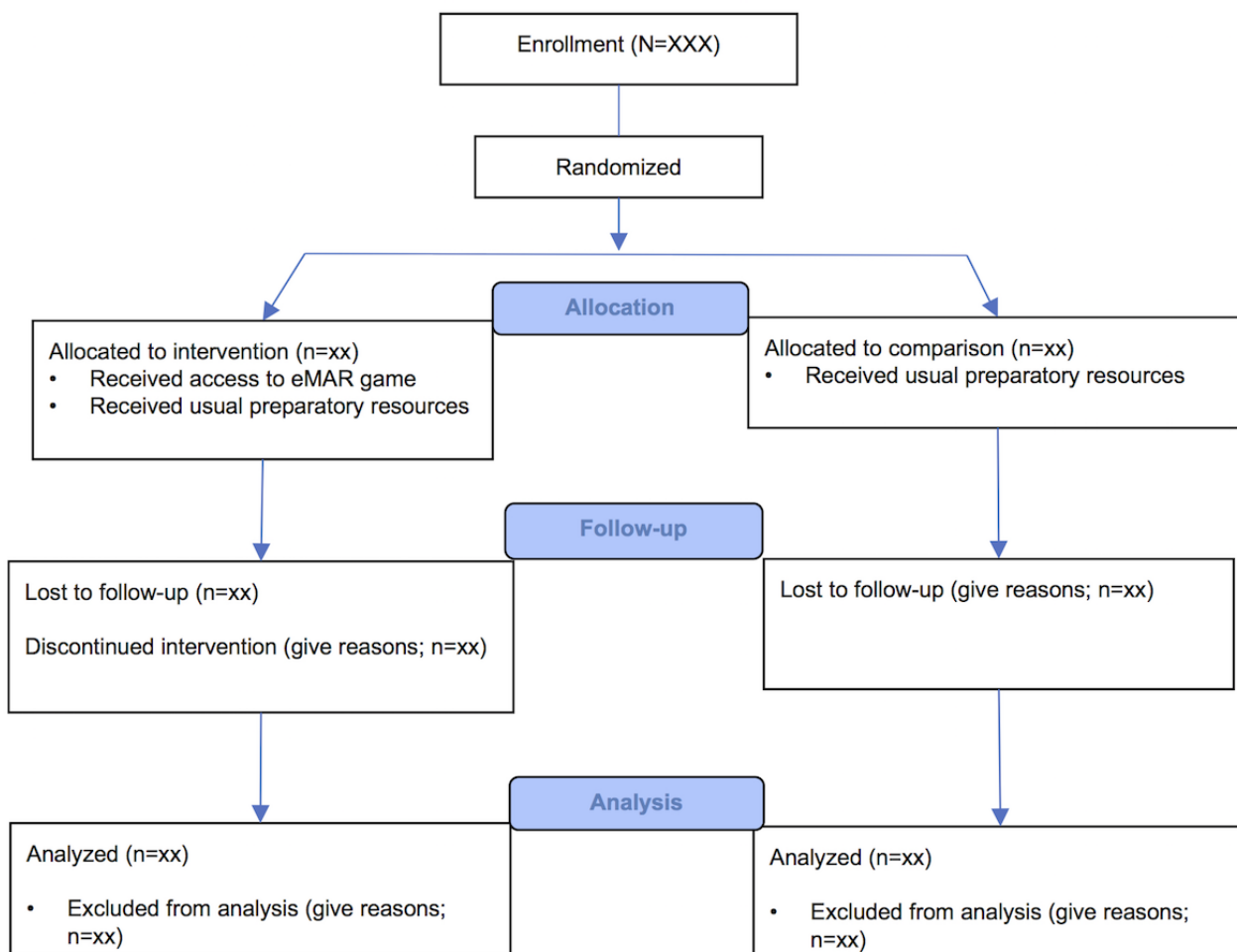
Phase 2

The specific questions to be asked during focus group interviews with participants will be informed by the preliminary quantitative findings [35]. Although emergent and contingent on the quantitative findings, it is expected that a range of qualitative interview questions will be developed based on the core variables in part 1 of the study (ie, medication errors generated, self-efficacy and knowledge related to administration, etc). During these focus group interviews, participant feedback related to the usability, design, and user experience of the game will also be sought. Approximately 20 participants from either semester (both intervention and control groups) will be interviewed in the qualitative phase of this study (week 9).

Data Analysis

Phase 1

Survey data will be analyzed through descriptive and inferential statistics. Student *t* test to compare pre- versus postcontinuous outcomes for intervention and control groups in relation to number of medication errors or near misses, number of deviation from best practices, and length of time (efficiency) of administration will be completed.

Phase 2

Semistructured focus group interviews will be audio recorded and transcribed verbatim. A minimum of 2 researchers will conduct a directed content analysis [36] of the data; this will be triangulated with quantitative findings [37] to generate a deeper understanding of the effectiveness of the gamified eMAR simulation as a technology-enabled clinical education tool.

Ethics

Ethical approval for this study has been obtained from Western University, London, Canada (HSREB #109180).

Results

Preliminary results of half of the desired study cohort is expected in early 2018. By early spring 2018, the findings of the study in its entirety will be available. Currently, data collection of the fall 2017 cohort has concluded.

Discussion

Principal Considerations

Due to the pragmatic randomized controlled trial design, the findings of this study will establish baselines regarding the effects of serious gaming approaches toward improving nursing students' eMAR medication administration safety; similarly, the findings will also outline best practices toward the development of immersive gamified simulation opportunities that can be leveraged by other educational organizations. Given the lack of research and consolidated knowledge about this teaching-learning approach [38], both quantitative and qualitative findings arising from this study will provide important theoretical and pragmatic insights to others developing immersive simulation or virtual reality opportunities.

Although still an emerging area of research, there is growing interest toward the development of serious gaming or gamified approaches in clinical education [6,39,40]. Recent evidence suggests that gamified approaches in nursing education can offer a range of benefits, including anxiety reduction in students, improvement in the repeatability of skills, and increased access to learning opportunities [41,42]. Other nursing education research has posited that there is no difference between gamified learning versus face-to-face clinical simulation [43]. Medical education research has found largely positive results regarding the use of gamification as a teaching-learning mechanism, in terms of medical content validity [27], acceptance and retention of learned knowledge [44], and ongoing skill retention and learner engagement [29,45]. The growing importance and interest in this topic can also be inferred from the recent registration of a *Cochrane Database of Systematic Review* protocol, which plans to examine the effectiveness of serious gaming and other gamified interventions in health professional education [38]. As outlined by Cant and Cooper [41], this type of clinical education pedagogy will likely "have a major place in nursing curricula in the next decade," and therefore warrants further examination by clinician educators.

Strengths and Limitations

As a strength, this study will be one of the first appropriately powered trials of a serious gaming intervention in nursing education. Furthermore, the pragmatic randomized controlled trial design [46] with complementing qualitative elements will assist in generating informative insights related to the effectiveness of using a serious gaming intervention to educate students to the complexities of medication administration in an eMAR environment. Although this study has some strengths, there are some limitations that should be outlined. First, the observational method and environment for data collection raise the potential of an observer effect, in that participants may recognize they are being observed by members of the research team during their return demonstration of a medication administration scenario in the CSL. Second, the variability in data collection by multiple observers may be a potential limitation. Although standardized observation guides and training will be provided to the data collectors, interrater reliability between observers may be a source of study error. Finally, given the structure of the game, it is not possible to fully ascertain whether there is a dose-response relationship between cumulative gameplay time and its effect on medication error frequency rates. As the eMAR simulation game offers the player a fair amount of autonomy to make errors and experiment with different actions and processes, any linear relationship examined between overall gameplay time of a participant and their medication error rate may not be an accurate depiction of medication administration knowledge or comprehension.

Conclusions

Given the potential severity of health outcomes caused by medication errors, nursing education continues to place emphasis on simulated clinical education to provide students with the necessary clinical skills related to medication administration before direct interaction with real patients. Simulation has been widely adopted within clinical education to support medication

administration education. However, because of financial and resource constraints experienced by educational institutions, opportunities for students to meaningfully practice eMAR administration continue to be limited. The development of innovative clinical learning strategies such as serious gaming and gamification may offer new opportunities for students to learn these important skills and develop clinical judgment. The findings of this study will generate evidence of a gamified approach to learning in nursing education and provide new pedagogical implications to prepare students with the appropriate skills, knowledge, and competencies related to electronic medication administration.

Acknowledgments

Conflicts of Interest

None declared.

Multimedia Appendix 1

Funder feedback.

[PDF File (Adobe PDF File), 80KB - resprot_v7i5e138_app1.pdf]

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Abbreviations

CSL: clinical simulation laboratory
eMAR: electronic medication administration record
SMART eMAR: a physical, simulated eMAR system used within the university's CSL

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Protocol

Integrated Models of Care for People Living with Hepatitis C Virus and a Substance Use Disorder: Protocol for a Systematic Review

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Abstract

Background: People living with a substance use disorder (SUD) are a key population within the hepatitis C virus (HCV) epidemic. While integrated and community-based models of care have shown positive outcomes among this population, the literature has been primarily focused on the HIV context. This paper outlines a systematic review protocol on the impact of various integrated models of care, which includes HCV and SUD services, on various treatment, and health-related outcomes among this population.

Objective: The objective of this review is to determine the impact of integrated models of care on HCV and addiction treatment and health-related outcomes for adults living with HCV and an SUD.

Methods: We will search 5 databases, article reference lists, and abstracts from relevant conferences that investigate the impact of integrated models of care on treatment and health-related outcomes among people living with HCV and an SUD. Database searches will be conducted and titles, abstracts, and the full-text of the relevant studies will be independently reviewed in separate stages. The methodological quality of included studies will be assessed using a validated tool. Data from included articles will be extracted using a standardized form and synthesized in a narrative account.

Results: For this project, we have received funding from the Canadian Institute of Health Research. To date, we have completed the search strategy, reviewed the titles, abstracts, and full-texts. Grading the selected studies and qualitative synthesis of the results are currently under way, and we expect the final results to be submitted for publication in the fall of 2018.

Conclusions: The systematic review will describe different integrated models of care that could be effective in improving the health and well-being of people living with HCV and an SUD. Results of this review could also identify quality improvement strategies to minimize the health and cost burden imposed on patients, healthcare professionals, and the healthcare system.

Trial Registration: PROSPERO CRD42017078445; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=78445 (Archived by WebCite at http://www.webcitation.org/6z4YnkE9G)

(JMIR Res Protoc 2018;7(5):e122) doi:10.2196/resprot.9532

Introduction

People living with a substance use disorder (SUD) are a key population within the hepatitis C virus (HCV) epidemic. Specifically, the estimated global HCV prevalence among people who inject drugs (PWID) is 67%, or approximately 10 million individuals, with incidence rates ranging from 5% to 45% per year [1]. PWID constitute approximately 14% of the 71 million people infected with HCV globally [2]. Due to similar transmission routes, there is overrepresentation of PWID among

individuals who are co-infected with HCV and HIV, with over half of the 2.3 million globally co-infected individuals being among PWID [3,4]. PWID are not only at greater risk of HCV infection (and re-infection), but also at increased risk of disease progression, mortality, and onward HCV transmission due to various socio-structural and environmental exposures, including poor access to health care services, socioeconomic marginalization, and the persistence of law enforcement-based responses to illicit drug use [1,5-7]. While HCV is mainly transmitted via injection drug use, non-injection drug use has also been associated with HCV infection. For example, there is some evidence of HCV transmission via crack pipe sharing [8], and among men who have sex with men who use non-intravenous drugs [9,10]. HCV prevalence is higher in non-injecting drug users than in nondrug users. Moreover, many PWID are polysubstance users with non-injection drugs [11].

Despite the advent of safe and highly efficacious direct-acting antiviral–based therapy, resulting in the possibility of controlling the HCV epidemic, concerns regarding treatment access, adherence, and potential reinfection, particularly among marginalized populations such as PWID, remain [5,6]. Indeed, access and uptake of HCV treatment has been consistently low among PWID, with studies indicating that only 1%-6% of this population has ever been treated with interferon-based therapies [12-14]. The reluctance of physicians to treat HCV infection in PWID is likely due to the stigma and discrimination that continue to persist among this population [15]. Low treatment rates among this population may also reflect PWIDs' fear of treatment, competing priorities (eg, active illicit drug use), as well as general barriers to accessing healthcare [16,17]. Moreover, in some jurisdictions, the high cost of direct-acting antivirals (DAA) treatment is only covered provided that the patient meets specific criteria (eg, a fibrosis score of 2 or more) [18]. As such, the high cost of DAA may also constitute a barrier to treatment for PWID who do not meet these criteria, or who live in settings where DAA treatment is not covered. Nevertheless, recent studies have shown that, when appropriately supported, PWID are able to achieve similar rates of sustained virologic response compared to the general population [19,20].

Prior reviews have explored integrated models of care in the context of HIV, and these have been shown to have a significant beneficial impact on the treatment and health outcomes of PWID, particularly when coupled with SUD services [21]. Similarly, emerging studies have suggested the importance of opioid agonist therapy (OAT) and mental health services on reducing the risk of HCV reinfection among this population [19,22-24]. However, there has been no explicit systematic review conducted on the impact of HCV and SUD integrated programs and services on HCV, and addiction treatment and health outcomes among individuals living with these comorbid diseases. This review will address an important gap in the literature by comprehensively assessing the available literature to provide insight into effective and efficient models of care for people living with HCV and SUD.

Methods

The current protocol has been registered in the PROSPERO CRD42017078445 and conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist (Multimedia Appendix 1). We will also adhere to the PRISMA guidelines for the development of this systematic review report [25].

Research Question

The proposed systematic review will synthesize the existing literature on HCV and SUD integrated models of care to date. Specifically, this review aims to answer the following research question: what is the impact of integrated models of care on HCV and addiction treatment outcomes (eg, HCV treatment adherence, OAT uptake), health-related outcomes (eg, HCV clearance), and cost-related outcomes (eg, long-term cost effectiveness) for adults living with HCV and an SUD?

Eligibility

Original quantitative and qualitative research studies that reported on integrated care models for adults living with HCV and an SUD will be included. For the present study, substance use will be defined as any use of alcohol, illicit use or misuse of opioids (eg, heroin, prescription opioids, methadone, morphine, oxycodone), or stimulants (eg, cocaine, methamphetamine). We will include studies that describe service integration interventions at varying degrees of integration. Some examples may include HCV screening or treatment within OAT clinics or multidisciplinary care addressing medical, psychological, social, and addiction-related needs.

Commentaries, letters to editors, editorials, and other types of opinion pieces will be excluded. Literature reviews will also be excluded; however, we will conduct back referencing to ensure that all relevant studies from the literature review are captured. The search will not be restricted to setting. Moreover, we will not exclude studies based on study design, but the degree of bias will be noted in interpreting the findings. The search will be restricted to publications in English, French, and Spanish.

Information Sources and Search Strategy

A comprehensive search strategy to identify documents that met the eligibility criteria will be conducted. Specifically, the databases MEDLINE, EMBASE, CINAHL, PsycINFO, and Web of Science will be searched with no date restrictions in order to acknowledge changes in care over time. However, we will ensure that the study period is included in our analysis. In addition, we will search ClinicalTrials.gov to ensure that we capture studies that have not yet been published. Consistent with similar reviews [21], search terms will include those that are related to three themes, namely HCV, substance use, and integrated healthcare services, and these terms will be mapped to database-specific medical subject headings and controlled vocabulary terms when available (Multimedia Appendix 2).

To maximize the number of included studies, hand-searching of full-text scientific conference proceedings from HCV- and substance use conferences (eg, American Association for the Study of Liver Diseases, European Association for the Study

of the Liver, Conference on Retroviruses and Opportunistic Infections, International AIDS Society Conference) will be conducted and will be restricted to be within the previous two years. We restricted the conference abstract search to the past two years in order to limit duplication with older abstracts that may have been published as academic articles. We will also search reference lists of research articles and reviews by hand to identify relevant articles not otherwise captured. These search methods have been developed in consultation with a medical reference librarian with expertise in systematic reviews and population and public health at the University of British Columbia (U. Ellis, personal communication, June 12, 2017) and will be executed by an author experienced in conducting systematic reviews.

Study Records

Database searches will be conducted and the abstracts and full-text articles from the search strategy will be imported into Endnote X7. After removing duplicates, the titles, abstracts, and full text of articles will be independently reviewed in three separate stages by two research team members. The first stage will consist of reviewing the titles. The second stage will consist of reviewing the abstracts. The third stage will be the review of the full text of the articles. At each review stage, studies clearly not meeting the inclusion criteria will be excluded from further review and the reason for exclusion will be recorded. Any disagreements between the two investigators will be resolved by discussion with a third investigator.

Risk of Bias in Individual Studies

The methodological quality, including risk of bias, of included quantitative research studies will be assessed using a modified version of the Downs and Black checklist for the reporting of healthcare studies, which has been shown to be a valid and reliable tool [26,27]. Higher scores out of a total score of 18 represent higher overall methodological quality. Qualitative studies will be assessed using the Critical Appraisal Skills Programme tool [28], a widely used tool recommended by some journals [29]. Each study will be scored by one investigator and verified independently by a second investigator. Where there were disagreements in scoring, this will be resolved by discussion with a third investigator.

Data Synthesis

Following PRISMA guidelines, a flow chart of the selection process will be produced. Additionally, data from included studies will be extracted using a standardized form developed to capture study characteristics and main findings and summarized in a table, including information on: study characteristics (eg, study setting, study design, study period, and study population), participant characteristics (eg, age, sex or gender), study objectives, integrated service intervention type and type of facility, and main study findings. Findings from the included studies will then be synthesized in a narrative account that addresses the objectives of this systematic review.

Results

We have received funding from the Canadian Institute of Health Research, allowing the commencement of the project. To date,

we have completed the search strategy. We obtained 1711 records after duplicates were removed. After screening the titles and abstracts, 153 full-texts were reviewed. Of those, 57 were excluded and 96 will be included in the qualitative synthesis. After hand-searching conferences abstracts, 36 were selected for inclusion. We are currently in the process of grading the selected full-texts, and qualitative synthesis of the findings is currently under way. We expect the final results to be submitted for publication in the fall of 2018.

Discussion

To our knowledge, this systematic review will be the first to synthesize the available evidence on the integration of HCV and substance use services on treatment, health, and cost-related outcomes. Identification and implementation or adaption of different integrated models of care to improve the health and well-being of people living with HCV and an SUD may have a significant impact on reducing the negative health and social consequences associated with these comorbid diseases, as well as healthcare utilization costs, and resource burden on the healthcare system. The results of this systematic review may guide future research in this area and contribute to the development of evidence-based policies and programs for the treatment and care of people living with HCV and an SUD.

We plan to implement a comprehensive end-of-project knowledge translation strategy to ensure that the findings of this research are accessible to key stakeholders. Specifically, we will present the results of this review at relevant HCV and substance use meetings nationally and internationally, as well as publish in an open access peer-reviewed journal in an effort to increase access for appropriate scientific, clinical, and public audiences. Lastly, we plan to collaborate with relevant clinical programs and community organizations to ensure the timely and effective application of the research findings. Specifically, we will organize plain language presentations of our research findings with time for discussion and feedback, we will attend meetings and planning discussions with health authorities and health administrators, and we will reach out to policy-makers via briefing notes or other venues.

There are several limitations that should be noted. The expected heterogeneity of the literature on integrated models of care may affect our ability to draw clear conclusions from the literature. Additionally, we recognize that the selection and qualitative synthesis of the eligible studies is a subjective process; however, we will seek to minimize this limitation by duplicating our search and utilizing two reviewers to conduct the screening and quality assessment processes independently. As with all reviews, it is possible that some eligible studies may be missed in our search strategy. To minimize this limitation, we have kept our search strategy relatively broad and have sought input from an experienced librarian. Lastly, there may be a publication bias observed as a general limitation of systematic reviews. We will try to minimize this issue by searching databases for unpublished studies (eg, ClinicalTrials.gov).

In sum, this systematic review will synthesize the available evidence on the integration of HCV and substance use services and its impact on various outcomes, including health- and

cost-related outcomes. It is expected that the findings from this review will provide evidence towards the effective delivery of healthcare programs and services for people living with HCV and an SUD.

Authors' Contributions

LT and MES designed the systematic review protocol, with support of a health librarian. LT prepared the first draft. MES and SP reviewed and revised the first draft. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist.

[PDF File (Adobe PDF File), 116KB - resprot_v7i5e122_app1.pdf]

Multimedia Appendix 2

Search Strategy in OVID MEDLINE.

[PDF File (Adobe PDF File), 219KB - resprot_v7i5e122_app2.pdf]

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Abbreviations

DAA: direct-acting antivirals
HCV: hepatitis C
OAT: opioid agonist therapy
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PRISMA: people who inject drugs
SUD: substance use disorder

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Proposal

User Participation in Coproduction of Health Innovation: Proposal for a Synergy Project

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Abstract

Background: This project concerns advancing knowledge, methods, and logic for user participation in coproduction of health innovations. Such advancement is vital for several reasons. From a user perspective, participation in coproduction provides an opportunity to gain real influence over goal definition, design, and implementation of health innovations, ensuring that the solution developed solves real problems in right ways. From a societal perspective, it's a mean to improve the efficiency of health care and the implementation of the Patient Act. As for industry, frameworks and knowledge of coproduction offer tools to operate in a complex sector, with great potential for innovation of services and products.

Objective: The fundamental objective of this project is to advance knowledge and methods of how user participation in the coproduction of health innovations can be applied in order to benefit users, industry, and public sector.

Methods: This project is a synergy project, which means that the objective will be accomplished through collaboration and meta-analysis between three subprojects that address different user groups, apply different strategies to promote human health, and relate to different parts of the health sector. Furthermore, subprojects focus on distinctive stages in the spectrum of innovation, with the objective to generate knowledge of the innovation process as a whole. The project is organized around three work packages related to three challenges—coproduction, positioning, and realization. Each subproject is designed such that it has its own field of study with clearly identified objectives but also targets work packages to contribute to the project as a whole. The work on the work packages will use case methodology for data collection and analysis based on the subprojects as data sources. More concretely, logic of multiple case studies will be applied with each subproject representing a separate case which is similar to each other in its attention to user participation in coproduction, but different regarding, for example, context and target groups. At the synergy level, the framework methodology will be used to handle and analyze the vast amount of information generated within the subprojects.

Results: The project period is from July 1, 2018 to June 30, 2022.

Conclusions: By addressing the objective of this project, we will create new knowledge on how to manage challenges to health innovation associated with the coproduction process, the positioning of solutions, and realization.

Introduction

Health innovation refers broadly to products, services, organizations, and dissemination of new knowledge that affects people's ability to maintain and promote their health and well-being as well as prevent ill health [1]. Health as an arena for innovation is connected to the need for structural transformation because of increased demands on health care by medical advances, changes in diagnostic systems, and an aging population [2-4]. An important principle to guide this transformative process involves targeting individual

responsibility or cooperation and is expressed in discourses and practices aiming at "person-centered care" [5]. But despite extensive investments to strengthen the role of the patient or care recipient, health innovations seem difficult to implement in established care settings [2,6].

The Swedish Agency for Health Technology Assessment and Assessment of Social Services [7] highlights the prolonged time it takes before research is put into practice and the lack of influence from patients, clients, and practitioners in formulating the aims of the research. In turn, the Swedish Agency for Health and Care Services Analysis [8] points to problems concerning the implementation of the new Patient Act from 2014, which aims to strengthen the patient's position through participation in their own health care. Moreover, reports point out difficulties in translating the act into practice because of lack of knowledge and concrete tools to fulfill its intentions. As a consequence of these findings, the Swedish Government promotes "applied welfare research" conducted in cooperation with clients or users as well as practitioners to increase the utilization of knowledge for the people affected by the research question [9].

As for industry, the growing and changing health sector is an arena with considerable potential for innovation and the development of new services and products as well as novel business models; however, the health sector is complicated and difficult to navigate [10]. It is a highly regulated sector with complex ethical dimensions to understand and manage [11]. In addition, services and products for the public health sector need to be validated and verified, and this is a costly and time-consuming process [12]. Another obstacle is the Public Procurement Act, which complicates cooperation between public actors and companies. As a result, the industry selling services and products to the public health sector seldom has a direct relationship with the end user, making it difficult to develop user-centered health innovations [13]. In addition to these aforementioned barriers, there are weaknesses in the design and methods for participation currently used in the health sector [14,15]. A common practice is to use user participation in evaluation but not in the development of products and services, which frequently results in an end product that does not correspond to the needs and wishes of the user group.

Research has shown that companies that interact with users of their products for knowledge exchange benefit from reduced uncertainty regarding demand conditions, are more innovative, and more likely to develop products that will succeed in the market [16-18]. This synergy project creates knowledge that can be used to develop future products and services to be offered to a larger market beyond the scope of the synergy project alone. Taking users as a starting point facilitates the customization process, providing opportunities for the users to gain a product that meets their needs while allowing companies to avoid transaction costs related to transferring customers' requests collected via surveys and other means [19].

Fundamental to this synergy project is that innovation needs to be seen as a process or spectrum ranging from problem elicitation to implementation and dissemination (Figure 1). To meet the described problems and challenges, the synergy project is founded on a model for coproduction where industry and the public sector participate together with users throughout the innovation processes. The purpose of early coproduction with users is to create solutions that are driven by the users and that meet their actual needs. It also creates *one* integrated process where quality assurance, in the form of validation and verification, and implementation is achieved as part of the innovation process—and not afterward as a costly and time-consuming additional process. The main research question of the project is: *How can user participation be applied to overcome barriers in the coproduction of digital health innovations—in the spectrum from problem elicitation to implementation?*

By addressing this, our goal is to create new knowledge of how to manage challenges to health innovation that are associated with the coproduction process, the positioning of solutions, and realization.

User-Centered Innovation, Coproduction, and Digitalization

Innovation studies, in general, and health innovation literature, in particular, point out different types of innovations, such as new products, services, processes, methods, markets, and sources of supply [4,20,21]. New procedures, health policy innovations, and strategy innovation are also defined as special types of innovation in relation to health [4]. In each of the subprojects, a new digital health innovation is developed. However, the focus of the synergy project is not on the innovation as such (end result), but on the process of coproduction in which health innovations are designed, developed, and disseminated.

There are many different models of innovation, developed for diverse purposes and aiming at various levels of aggregation. A linear—technology-push—model of innovation conceptualizes innovation as a process triggered by accomplishments in research and development that through production and marketing lead to a commercialized product on the market [22]. According to a chain-linked—market-pull—model of innovation, innovation emerges when the potential in the market has been identified and developed through constant feedback between design, test, and market units, which are embedded in research and knowledge environment [23]. More recent models of innovation put even higher emphasis on the interactive nature of the innovation process, not least arguing for the users as important partners for collaboration in innovation [24,25]. The system of innovation approach views innovation as a cumulative process emerging through systemic interactions of the actors (firms, research organizations, governmental authorities, and customers) embedded in a certain institutional setting, delineated by regional, national, or sectorial boundaries [26-28]. In this literature, users can be viewed as sophisticated buyers, active codevelopers, and value setters, contributing to structural change processes [29]. In our project, we view innovation as a circular process with 4 related stages—solution, output, outcome, and impact (Figure 1). The impact stage describes the process of defining a problem together with users and other stakeholders in relation to a challenge that can be addressed through the introduction of a new innovation.

Figure 1. The health innovation process, with 4 stages of value creation—solution, output, outcome, and impact—expressing the logic of change.

The solution stage describes the design of strategies for how a solution to the defined problem can ground challenges in logical frameworks or theories of change that could be used in the design of solutions together with users and other stakeholders. The output stage describes the process of knowledge, service, and technology development in coproduction with various stakeholders and the implementation of the developed artifact, guided by models and methods for intervention and change management and for evaluation. The outcome stage describes the evaluation of effects of implementation in relation to the defined problem and thereafter dissemination of the results. This includes a critical analysis of the direct and indirect consequences of dissemination and how it contributes toward impact in relation to the initially identified problem. This model, with its 4 stages, has been developed as a part of strategic work to define health innovation efforts at Halmstad University [30]. It goes beyond technology-push or market-pull dichotomy,

highlights the iterative nature of innovation, and suggests that innovation can be triggered at any stage of the process. It is inspired by an interactive approach to innovation, emphasizing collaboration with different stakeholders at each stage. In this synergy project, we want to advance our understanding about one type of stakeholders—users; more concretely, we are interested in finding under which circumstances and what roles different groups of users play under different stages of a health innovation process as well as to analyze challenges and mechanisms related to their inclusion. Thus, we are interested in user-centered innovations which we define as triggered by unique user needs and developed in collaboration with product or service providers, public sector, and researchers. Including users and other stakeholders of health products and services in the design and development process leads to increased efficiency and quality of health care processes [31,32].

Various concepts, such as cocreation, codesign, and coproduction, are used to describe innovation processes with several stakeholders involved. Sometimes they are used as synonyms, and sometimes differences are pointed out [33]. Cocreation is the broadest term, including different forms of interaction with users (or other stakeholders) from consultation to participation and generation [34]. Codesign refers to the "creativity of designers and people not trained in design working together in the development process" and focuses on the early stages of the innovation process from idea generation to product development and less so on implementation, dissemination, and evaluation [33]. In this project, we follow Dunston et al's (2009) understanding of *coproduction* in health, which implies that health innovation evolves in a collaboration process between users, health care professionals, and other stakeholders, such as private companies bringing products and services to the market and researchers at the University [32]. This concept is chosen because it is best aligned with the understanding of the innovation process that is used in this project. It also delineates interaction with users as an active collaboration rather than opening up for any type of activities where users influence innovation processes.

According to health care and innovation scholars, one of the biggest potentials for renewal of the health sector is via *digitalization*, which also has considerable potential to result in cost savings [2,35]. In the Swedish context, it is estimated that digitalization of health care could save 180 billion SEK a year [36]. Furthermore, the use of digital technologies could also lead to better disease prevention, greater personal engagement in one's health, and an improved work environment for health care professionals [36]. Thus, because of its high innovation and value-added potential, we focus on digital, user-centered health innovations. In this project, we understand digitalization as the use of a variety of converging digital tools (wireless sensors, information systems, social networking, and mobile connectivity) in health-related products and services (see also [2]).

Subprojects

The synergy project consists of 3 subprojects, allowing us to study user participation and coproduction in different organizational contexts and in relation to different user groups and, thus, to address coproduction-related challenges from different perspectives. Although the projects have a similar emphasis on user participation in coproduction, they also target distinctive phases or segments in the spectrum from problem elicitation to the implementation of health innovation (Figure 1). Implementing these projects in parallel will help gain an in-depth understanding of the challenges and barriers associated with user-centered coproduction and how these barriers can be overcome or managed during the innovation process. The projects are similar in that they are addressing complex health challenges and are designed so that users and other stakeholders have significant influence over the content of the projects. Collectively, our proposed projects are likely to yield new knowledge of these challenges and how to tackle them from a holistic perspective, rather than from a segmented process of innovation.

The project is generic in its ambition to create a meta-framework for solutions to problems that currently exist in the health sector, which transcend the boundaries of each subproject. By studying similarities and differences in our chosen areas of innovation—such as different social and organizational contexts and the needs, abilities, and conditions of different user groups—we will generate knowledge and solutions to creating health innovations that can be applied across a variety of contexts. The research question is multidisciplinary and needs an integrated effort from competencies belonging to different research fields to be answered. Moreover, the project aims at mobilizing researchers and representatives from industry, the public sector, and users in project teams, conducting health innovation in an integrated participatory design process where all actors are involved in the process at all stages.

Project 1: Better Health With Smart Participation

Digital communication tools through coproduction with children in habilitation target challenges in coproduction where children participate in the development of digital health, promoting services in relation to their own health. The context for application of such services is, in this case, health care and habilitation for children with disabilities. In relation to our model for innovation (Figure 1), the project specifically aims to strengthen coproduction with children in problem elicitation, design, development, and implementation.

Project 2: Easy Life With 3D

Personalized assistive devices through coproduction with people with functional disabilities address our identified challenges by applying coproduction in digital visualization technology and rapid prototyping, at the Fab Lab facility at Halmstad University. The products coproduced target people with functional disabilities and are primarily concerned with the development, implementation, evaluation, and dissemination stages in the innovation model (Figure 1).

Project 3: The GoodLlife at Home in Old Age

Intelligent age–friendly homes through coproduction with elderly people address the research question by providing an understanding of challenges for coproduction in the contexts of people's own home environment and in relation to home care. The target group is the older people, and the aim of the project is to coproduce innovative solutions to strengthen the possibility to remain at home and gravitates mainly around the steps of implementation, evaluation, and dissemination in our model for innovation (Figure 1).

Work Packages

Our rationale for this synergy is that the integration of users in the coproduction of health innovations contributes to relevance and quality of innovations as well as to efficiency in the innovation process. However, achieving such user participation can be challenging both in itself and because of circumstances and practices associated with various contextual factors. We have specifically identified 3 areas of challenges, namely, *coproduction*, *positioning*, and *realization*. These challenges are influenced by factors associated with different contexts and user groups, and therefore need to be studied from a variety of perspectives to create a broad understanding of the meaning of

the challenges and how they can be managed at a general level. We intend to accomplish this by integrating 3 subprojects that focus on different user groups, apply different strategies to promote human health, and relate to distinct parts of the health sector.

Work Package 1—Coproduction

The coproduction work package targets how problem formulation and development of a logical rationale for health innovation is in need of early collaboration with users. It also deals with barriers to designing health innovations with vulnerable groups. The work package is divided into 3 parts:

- *Method for early collaboration with users:* Design a method for early user involvement in problem elicitation from which a rationale and logic for health innovation can emanate.
- *Framework describing barriers:* Identify barriers to working with vulnerable groups to bridge the gap between users, industry, health professionals, and researchers.
- *Conditions for coproduction:* Pinpoint problems relating to questions of ownership, ethics, and legal matters in the coproduction of products and services in the health sector, including experiences of the view of users, industry and public sector representatives, and researchers.

Work Package 2—Positioning

The positioning work package is focused on the strategic adaptation of health innovation in relation to laws and regulation in the health sector, existing organizational contexts, and routines to prepare for future implementation. It draws on the experiences from the 3 subprojects to develop generic strategies for how and when to introduce health innovations based on user needs and perspectives as well as contextual factors relevant to other stakeholders:

- *Regulatory framework:* Create a framework for prospective adaption of health innovations to fit laws, regulations, and ethical dimensions in the health sector to facilitate future implementation.
- *Planning model for implementation:* Create a method-driven and generic model for how to work with the prospective adoption of health innovations to tackle barriers for implementation related to organizational contexts, routines, hierarchy, and inertia in systems.
- *Patterns of onboarding:* Develop a methodology that can be used generically to establish where in an existing ethical, regulatory, and organizational framework health innovations have potential to be introduced and identify actors that play a key role in facilitating service onboarding and use.

Work Package 3—Realization

The realization work package aims to frame strategies for successful implementation, evaluation, and dissemination of health innovations that are coproduced with users:

- *Preservation of knowledge:* Establish design tools that convey the knowledge, values, and qualities originating from user participation in coproduction to be integrated into new solutions and to make sure that this information is preserved and continues to convey users' perspectives in future refinement or development of the innovation.

- *Framework evaluating implementation:* Use existing models for process and impact evaluation of implemented health promotion interventions as the basis for developing a broad evaluation framework that takes into account user perspective in evaluating implementation.
- *User-centered business models:* Increase knowledge on how to combine profitability and user value into viable business models for coproduced health innovations and how these issues can be dealt with already at the problem elicitation and design phases of the innovation process.

Methods

Overview

The synergy subprojects are designed in such a way that each of them can be carried out independently of the others. The subprojects use a variety of methods to generate empirical data adapted to circumstances and conditions for the individual project, and to the different phases of the innovation process (Figure 1). In identifying challenges and problems for the involved user groups, individual and focus group interviews will be conducted, as well as observation of users in the context of their everyday life. In the phase of creation of health innovations, the workshop format plays a significant part, and using a mixture of methods—storyboards, scenarios, analogies, etc—user groups, researchers, and company representatives work together iteratively to find solutions to identified problems. To evaluate outcomes of implementation and interventions, both quantitative and qualitative methods are used, in the format of validated questionnaires as well as individual and focus group interviews.

Data Collection and Analysis

The work on the work packages will use a case methodology for data collection and analysis based on the subprojects as data sources. Each subproject will be treated as a study object where documentation and results from the project will be used as data for qualitative analysis and design of frameworks and models that answer the goals described in the respective work packages [17,37]. A case study approach is beneficial in several ways for this project because it allows for a combination of data collection tools, gives attention to contextual factors regarding the phenomena under investigation, and can be used to develop theory [38]. Furthermore, in our ambition to develop a generic, as well as context-sensitive, understanding, the use of a multiple case study logic is vital. Our chosen cases (the subprojects) are similar in its attention to user participation in coproduction, but unlike regarding, eg, context and target groups. This allows for an examination of similarities and dissimilarities, patterns, and particulars in relation to each of the challenges (coproduction, positioning, and realization elaborated on in WP 1-3) and as such develops a generalized as well as context-sensitive understanding of user participation. The analysis of the research question at the synergy level will use strategies developed using the framework methodology to handle and analyze the vast amount of information generated within the subprojects [39]. This method uses matrices to summarize, compare, and synthesize diverse units for analysis.

Dissemination of Results

Coproduction in the health sector is complex, and the prerequisites and opportunities for coproduction are dependent on the target group, the type of innovation being developed, and the target health sector. Therefore, lessons learned from the respective subprojects will be shared to maximize the success of each project as well as to the overall synergy project. The results presented in the work packages will strengthen the ability for coproduction within the involved research groups, companies, public sector, and user associations, and this acquired expertise will, through established networks and collaborations, be disseminated to other researchers within and outside the University as well as to partners and the involved stakeholders. The work packages have 2 types of deliverables. *Reports* are small publications or presentations aimed at (1) spreading experiences, methods, and new knowledge between the 3 subprojects and the participating partners from industry and the public sector early in the course of the project and (2) making sure that the knowledge generated in the project remains with the project partners beyond individuals. For some work packages, preliminary reports will be released early internally and then completed as final reports for dissemination outside the synergy project group, such as to interested recipients within industry, public sector, and nongovernmental organizations. Such dissemination can be in the forms of presentations, popular science articles, information booklets, news articles to be spread via conferences, industry breakfast meetings, industry magazines, specialized websites, social media, and other relevant mediums. In addition to researchers, representatives from companies, public sector, and user organizations will be involved in these dissemination tasks. *Papers* are in the format of in-depth research publications based on the various reports and are developed to meet criteria for scientific evidence.

Project Organization

The synergy project team will be responsible for coordinating and addressing the main research question with its work packages, but collaboration with companies and users will be paramount at this level, and not only in the subprojects. This collaboration at the synergy level will be organized in the format of workshops involving researchers, companies, and users. At these workshops, preliminary results and findings will be discussed and elaborated and function as a springboard to achieve deliverables in the form of reports and papers. An essential objective of these workshops is to identify novel knowledge that constitutes intellectual assets, such as scientific results, methods, and inventions, and how to use them for various purposes. To manage questions of ownership and availability, the Intellectual Asset Inventory will be used (Chalmers Innovation office [40]).

Results

The project period is from July 1, 2018, to June 30, 2022. Outputs from the work packages will be reported continuously throughout the project period, such as internal reports, films, posters, exhibitions, prototypes, press releases, and finally as research publications.

Discussion

In this synergy project, we want to advance our understanding about one type of stakeholders—users; more concretely, we are interested in under which circumstances and what roles different groups of users play under different stages of a health innovation process as well as to analyze challenges and mechanisms related to their inclusion. This project contributes to the literature on health innovation in several ways. First, it provides an in-depth understanding on how user participation, and mechanisms for their inclusion, changes as the innovation process evolves, whereas most previous studies focus either on early stages of the process or verification. Second, the project places the user and the innovation process in a context, addressing the issues related to legal, ethical, and organizational aspects of the environment of coproduction processes, rather than focusing only on the added value of users' knowledge and ways to get access to it. Third, in this project, we focus on the coproduction with vulnerable groups of users such as children, older people, and people with disabilities. Previous research has shown the capability of these groups in participating in innovation processes as well as the added value of such participation [14,33,41]. This project will contribute to the research field by explicitly discussing mechanisms and challenges related to their inclusion.

Conflicts of Interest

None declared.

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<u>Proposal</u>

A Digital App to Aid Detection, Monitoring, and Management of Dyslexia in Young Children (DIMMAND): Protocol for a Digital Health and Education Solution

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Abstract

Background: Dyslexia, a specific learning difficulty and a disability as defined in the Equality Act 2010, is a lifelong condition that affects a child from the start of education. Dyslexia is characterized by difficulties in language processing (reading, spelling, and writing) which do not correspond with the child's general intellectual abilities. Although dyslexia cannot be cured, there is a consensus that interventions are more effective and have greater impact the earlier they are administered. Effective interventions start with diagnosis. Currently, formal diagnosis requires an assessment by a dyslexia specialist or educational psychologist. These assessments are expensive and are not easy for a non-specialist teacher or parent to interpret. Consequently, formal assessments are normally performed at a much later age, when interventions are less likely to be effective. Combining the latest in scientific research, expertise of dyslexia practitioners and real-time interactivity facilitated by digital technologies, we aim to provide a cost-effective and convenient solution that focuses on early dyslexia detection and management.

Objective: We discuss the rationale and protocol for the design and development of a digital health solution aimed at improving the early detection, monitoring and management of dyslexia (DIMMAND) in young children (4-8 years). The primary objective is to create a game-based digital solution aimed at children, parents, and teachers that firstly assesses, then monitors and manages progress in a convenient, cost-effective and private environment.

Methods: The proposed solution will be designed and developed in phases. In the initial phase, the full functional specification of the games that constitute the app will be designed, together with the overall architecture of the solution. Prototype proof-of-concept implementation for few of these games, and commercialization strategies will also be developed. The follow-on phases will see the design implemented into a validated solution.

Results: In the initial phase, we worked closely with dyslexia specialists, adult dyslexics, teachers of special-needs children, parents of dyslexic children, and senior dyslexia representatives for large organizations. These interactions provided insights into the range of language difficulties faced by dyslexics, which solutions are used by teachers and professionals, and an overall understanding of the market. We comprehensively defined the ethical, privacy, and data security issues. The detailed design spec of the games, the methodology to be followed to interpret the results, and flow diagrams illustrating how the game screens will be presented was completed. As proof of concept, a few reading, visual, and auditory games were developed and successfully tested by stakeholders on different digital devices. The stakeholders provided regular feedback and confirmed the viability of our game-based solution.

Conclusions: DIMMAND has the potential to provide significant positive health care and economic impact. It is expected to reduce intervention costs, improve dyslexia detection at an early age and aid self-management.

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Introduction

Developmental Dyslexia is a learning difficulty and a disability, as defined by the Equality Act 2010. It has serious short- and long-term effects that impact a child from the start of his or her education. Dyslexia is a lifelong condition [1-4], estimated to affect around 700 million people worldwide [2,5]. Dyslexia is characterized by difficulties in language processing (reading, spelling, and writing) which do not correspond with the child's general intellectual abilities [3,6]. In addition, dyslexia occurs across a wide spectrum, which makes it difficult to identify suitable customized interventions [4].

The neural basis of dyslexia is contested. Though there are likely many neurobiological factors contributing to dyslexia, several prominent theories identifying the main causal role have been proposed. The earliest theory was that dyslexia results from putative visual deficits, giving rise to difficulties with the processing of letters and words [7-9]. In the 1980s, dyslexia was reconceptualized as a weakness in phonemic awareness or letter-sound mapping, the foundation of reading for alphabetic systems [10-15]. This is by far the most popular theory and forms the basis for the majority of commercial assessment tools. It is, however, challenged on the premise that a more basic auditory deficit-impairment in the perception of short or rapidly varying sounds is the root cause [16,17]. Recent research suggests that visual-spatial attention skills are an excellent predictor of preschool children's future reading abilities [18,19]. Neuroimaging research in non-dyslexic adults shows widespread cortical activation during natural reading tasks, which overlap heavily with the visual maps that encode the visual space, auditory maps that encode sound frequencies, and the frontal regions of the brain [20,21]. Evidence from the scientific literature suggests that reading and writing difficulties can be caused by varied factors and successful interventions must therefore be customized to the individual's specific difficulty [22].

As mentioned previously, it is likely that varied neurobiological reasons manifest as dyslexia. It is therefore crucial to identify the individual's relevant strengths and weaknesses to provide the individual with effective customized support. Success with basic reading and writing is critical to overall success in life. Hence it is important to identify tailored strategies needed to help manage early learning processes that will ensure the individual receives the necessary attention applicable to their strengths and opportunities.

DIMMAND brings together all the scientific advances made in the field to date to provide a widely-available and cost-effective digital tool for the public use. We recognize the merit in each one of the above-mentioned theories, and acknowledge the need to bring them together under one coherent framework to detect the many different reasons why a child might be experiencing difficulty with reading and writing. The major goal of the project discussed in this paper is to devise a digital solution that will (1) help identify at a relatively young age (4-8 years) the nature of the literacy difficulty or difficulties the child experiences, and (2) propose tailored interventions to guide parents and less-specialized teachers to provide better support before the child experiences repeated failures.

The digital tool will feature innovative games that systematically explore a child's abilities in different aspects of reading and writing and their corresponding abilities in purely visual and auditory perception. Another important objective of DIMMAND is to help teachers or parents identify the most effective way to help a child as quickly as possible. Firstly, this is achieved by involving them in the testing process and secondly by providing customized intervention options which can be put into practice immediately. A key aspect of this app will be the inclusion of automated interventions, derived from existing research and educational strategies, to help identify which options, if any, will be beneficial to the child. Where an intervention is found to be helpful to the child, it will be incorporated into the presentation of rest of the app.

In the UK, dyslexia assessments are not available free of charge from the National Health Service (NHS). A professional assessment of dyslexia is expensive, costing upwards of £350. This assessment generally involves a session with a psychologist or dyslexia specialist who uses a combination of standardized tests to check the child's intelligence quotient (eg, Weschler intelligence scale for children [23]), reading, spelling, and writing abilities (eg, comprehensive test of phonological processing [24], wide-range achievement test [25], test of word reading efficiency [26]). Such assessments are carried out by educational psychologists or specialist teachers. Since it is not easy to diagnose with certainty a young child as dyslexic at the start of his or her education, these formal assessments are normally performed much later, after the child has been in school for several years and has presented with severe literacy difficulties. This is not ideal for a developing child, as it can affect self-confidence and may result in failure to fulfil their potential [6]. A few screening tools for young children are available such as Dyslexia Early Screening Test [27], Lucid Cops [28], and Dyslexia Quest [29].

DIMMAND differs from the existing solutions in two important ways. Firstly, the tests are structured in a bottom-up format and exploit the latest neuro-scientific evidence on dyslexia. Reading and writing are complex skills which involve visual, auditory, visuo-auditory, memory, and motor cognition. Our tests will systematically assess the various cognitive skills required for successful reading and writing. Secondly, inclusion of automated interventions enables the app to be more than a mere detection tool, by delivering dyslexia management at an individual level.

The rest of this paper presents the protocol for the proposed first phase of the project. In this phase, we will assess the feasibility of developing a digital solution for early identification of dyslexia. The key elements of the digital solution are: (1) to systematically assess the nature of literacy difficulties experienced by the child and (2) to propose tailored interventions.

Methods

Project Design

The proposed solution will be designed and developed in phases. In the first phase, the full functional specification of the test games that constitute the app were designed, together with the overall architecture of the solution. In addition, prototype proof-of-concept implementation for several of these games will be developed. The app design will be informed by insights provided by adult dyslexics, teachers and parents of dyslexic children, and by organizations and charities working in the field. The templates for user-engagement interviews are provided in Multimedia Appendix 1. Ethical and data management strategies have also been explored and will form part of the deliverables. Additional activities in this phase planned and underway include the development of a commercialization strategy for DIMMAND. In the follow-on phases, the design will be implemented into a validated solution.

App Development

The app will be developed with Unity [30], one of the world-leading cross-platform game development frameworks. Well established best-practice for software engineering will be followed. For example, a Model-View-Controller layer [31] will be used on top of Unity's built-in Entity-Component-System architecture [32] to maximize modularity and maintainability of the app.

This technology stack will allow our solution to be deployed and adapted to a variety of platforms including PC, Android, and iOS using a single code-base with minimal effort and without the need to write additional platform-specific code.

A user interface (UI) and story line will ensure the test presentation is engaging and stimulating for child users. The UI will be designed to be minimalistic, so as not to interfere with the testing itself, but at the same time it will be engaging to a young child.

At a high level, the system will comprise of a front-end and a back-end (Figure 1). The front-end includes the user-facing portions of the system; namely the app itself (for use by children) and the web-portal (for use by teachers and parents). The back-end will store and process data and will be where other important data and intellectual property not included in the client software, such as test generation algorithms, is stored. Front-end and back-end are completely independent and will communicate via the Web.

Figure 1. DIMMAND - System Architecture.
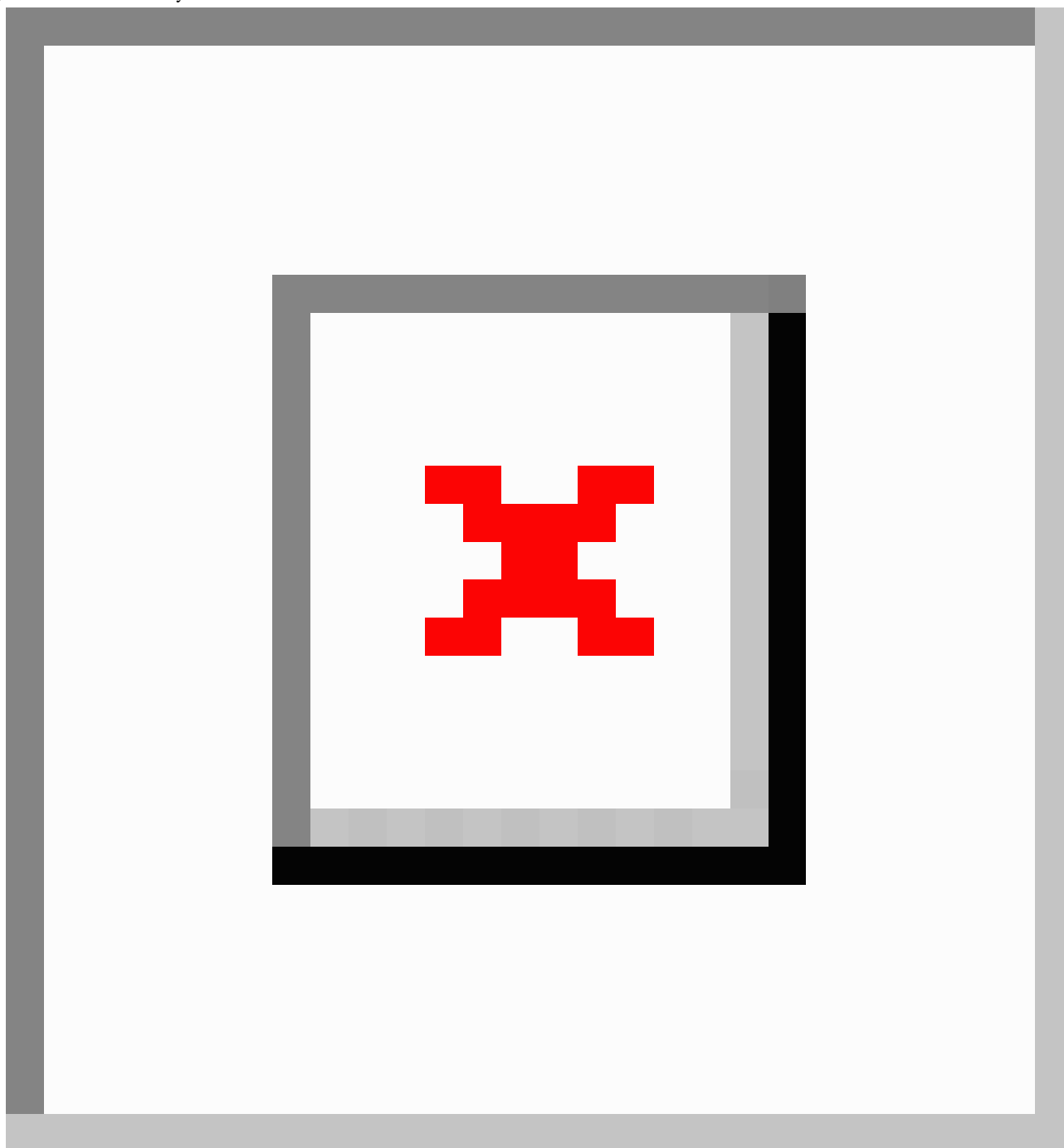
Expected Outcomes

During the first phase of the project, our Work Packages (WP) will deliver the following outcomes:

1. User Requirements Report (WP1): This will define the service and its underlying components. Stakeholders will be engaged in the design phase to understand the user's experience of the technology.

2. Report on Ethics, Legal, Data Security and Privacy Considerations (WP1): This will explain how the following issues are managed: informed consent, consideration of legislation, secure processing of personal data, etc.

3. Reading, Visual and Auditory Games Specification document (WP2): A detailed spec of the games, which will

be implemented. The games will systematically explore a child's capabilities in various aspects of reading/writing as well as in visual and auditory perceptions

4. Mock-up of the app with few concept games (WP3): User interfaces will be designed to show possible game flows and pages. The concept games will be developed using the cross-platform Unity framework.

5. Business Plan (WP4): This will include details on opportunity, vision and aim, market analysis and horizon scanning, target customers, business model, financials and follow on funding/investment, strategic analysis, intellectual property protection, and team.

In the follow-on phases, the design developed during phase one will be implemented into a fully-fledged app and validated

solution. This will include full-scale implementation of the games designed during phase one and include the design and implementation of the back-end database, data analysis, testing and validation with end-users, and productization of the solution.

Problems Anticipated

The following risks have been identified for the successful deployment of the solution.

- Games development (High). There is a risk that our games will not engage young children sufficiently. Since the games are intended to test the skills a child needs to read successfully, there is a challenge in finding the right balance between functionality of the game and an engaging user interface. This is a key challenge and it will be addressed via iterative user feedback.
- Data residency, hacking and privacy (High). App security will be embedded within our architecture and then validated and tested. We will ensure that both the app and data are secure at rest, in transit or in use. We will comply with the Data Protection Act (and the General Data Protection Regulation [GDPR] from 25 May 2018).
- Technology is new to the environment (High). Understanding the unique strategies to help a dyslexic child is traditionally carried out by attentive teachers in one-to-one settings. Utilizing technology to assist with special-needs education is an innovative concept. Achieving widespread take-up and effective use by end-users will require change management to be adequately supported.
- Ethical issues of unintended consequences (Low). Mechanisms to audit and monitor for these issues—and to mitigate them if found—will be developed during the prototype-development stage.

Ethics

For the initial phase of the project, user-engagement interviews were carried out to inform our approach to designing the test games. All interviewees who participated in the user-engagement phase of this project were given information about the project and their explicit consent was taken prior to the interview. The interview notes and transcripts were anonymized to safeguard the interviewees personal identity. The Caldicott principles [33] regarding patient-identifiable information will be continuously followed for the duration of the project.

Appropriate measures to address privacy and data security will be incorporated into our development plan. The architecture will embed app security and this will be validated and tested. This includes the design of our app and the selection of any servers (including cloud) with which the app will communicate. We will comply with the Data Protection Act from the moment data is obtained until the time when the data have been returned, deleted, or destroyed. Our servers will reside in the UK and European Economic Area (EEA) and no personal data will be transferred to a country of territory outside the EEA. Full compliance with the forthcoming GDPR and the existing Data Protection Act 1998 will be ensured. All ethical procedures in place will be detailed and documented as part of the deliverables for the first phase of the project, which will serve as the reference for the future development. Since the initial phase of the project did not involve research on human subjects, no ethical approval was necessary.

Results

The first phase of the app development commenced in March 2017. The results of the first phase will be utilized for the full-scale development of the solution. Additional publication is expected in early 2019.

Discussion

DIMMAND has the potential to provide a significant positive impact on health and education, and a positive economic impact. If each dyslexic child has access to a qualified, supportive, and attentive teacher, his or her potential to succeed in life is immense. However, unfortunately, that is often not the case. This makes the need for a widely available tool, such as the one proposed in this project even more urgent. This solution will assist a teacher or parent with no specialist knowledge of dyslexia to understand where the child is struggling (including whether it is a language-specific issue or related to general perception) and what kind of intervention will be most effective in helping the child. The games featured in the proposed app will be based on the range of scientific theories underpinning dyslexia. Overall, DIMMAND is expected to reduce intervention costs, improve dyslexia detection at an early age, and aid self-management.

Conflicts of Interest

AS and MRS are cofounders of Synergation Limited.

Multimedia Appendix 1

User engagement interview questions.

[PDF File (Adobe PDF File), 70KB - resprot_v7i5e135_app1.pdf]

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Abbreviations

EEA: European Economic Area
GDPR: General Data Protection Regulation
NHS: National Health Service
UI: user interface
UK: United Kingdom
WP: Work Package

Protocol

A Healthy Eating Education Program for Midwives to Investigate and Explore Their Knowledge, Understanding, and Confidence to Support Pregnant Women to Eat Healthily: Protocol for a Mixed-Methods Study

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Abstract

Background: Nutrition and healthy eating behaviors during pregnancy are vitally important for the health of a mother and her developing baby. However, some midwives have reported a lack of evidence-based nutrition knowledge for providing information about healthy eating to women during pregnancy.

Objective: In this study, the aim is to design and evaluate a healthy eating education program to enhance midwives' knowledge, understanding, and confidence to support pregnant women in South Australia to make healthy eating choices.

Methods: This mixed-methods study consists of two phases. The first phase, Phase 1, consists of an education program for midwives, "Healthy Eating in Pregnancy," to be delivered through a workshop or webinar. Each midwife will attend one workshop or webinar, which will be approximately two hours in length. This program will be evaluated through pre-, immediate-, and post-educational questionnaires utilizing a website specifically designed for this study. The participants will be midwives who are members of the Australian College of Midwives and the Australian Nursing and Midwives Federation, and users of social media (eg, Facebook and Twitter) residing and employed in South Australia. Phase 2 will consist of semistructured interviews with a purposive sample of midwives. These interviews will be undertaken to gain an in-depth understanding of midwives' views and how confident they feel educating pregnant women after receiving the healthy eating education. Interviews will be face-to-face or conducted by telephone with midwives who have participated in the healthy eating educational program.

Results: A systematic review has previously been undertaken to inform this study protocol. This paper describes and discusses the protocol for this mixed-methods study, which will be completed in April 2019.

Conclusions: The results from the systematic review suggest that there is clear justification to undertake this mixed-methods study to investigate and explore midwives' knowledge, understanding and confidence to support healthy eating in pregnant women. The results and conclusions from the systematic review provided some guidance for the design and development of this study protocol. This mixed-methods study will address a gap in the literature. The results from quantitative and qualitative data sources in this proposed study will help to draw conclusions to address the research topic.

Registered Report Identifier: RR1-10.2196/9861

Introduction

Overview of Influences for a Healthy Pregnancy

Cumulative evidence demonstrates a pregnant woman's health behaviors have a life-long influence on her health, and that of her developing baby. Good maternal and fetal outcomes have been associated with healthy nutritional habits and an active lifestyle during pregnancy [1,2]. Poor pregnancy outcomes such as preterm birth and small or large for gestational age are often associated with maternal body mass index disorders and life style choices, for example, being underweight or overweight, as well as smoking and alcohol consumption which are modifiable risk factors [3-6]. Unhealthy maternal behavior in pregnancy has been shown to have long-term effects on children and has been associated with conditions such as cognitive defects, obesity, asthma, and cardiovascular diseases [7-11]. Therefore, nutritional education during pregnancy has an important role in maintaining a healthy status for pregnant women.

Health Education During Pregnancy

Pregnancy is an opportunity to develop or maintain healthy behaviors, as most pregnant women will be motivated to gain more knowledge in order to give their developing fetus the best start in life [12]. Generally, midwives provide health education for pregnant women during antenatal visits. During antenatal visits, some women prefer verbal advice rather than written information from midwives [13]. It is good practice to first verbally discuss and give an explanation about healthy eating in pregnancy, followed by providing written information to help women understand more clearly. Therefore, written material is a complementary source of information [12]. Midwives have an important public health role and provide health education to pregnant women and new mothers.

Midwives' Public Health Role

National and international maternity policies value and support the role of midwives in public health [14]. Health care providers, such as midwives, have a unique opportunity to support women to make choices to promote health and prevent illness [14]. To achieve this goal the emphasis of midwifery policy and practice is to build relationships with the women they care for and to focus on health promotion as a holistic approach [14]. Therefore, the current study will examine the midwives' role to promote healthy eating, as well as develop and evaluate an educational program for midwives to complement their public health role.

Significance of Nutritional Health Education Programs

A systematic review is being conducted which aims to examine the effectiveness of healthy eating education programs for improving midwives' level of knowledge and confidence in promoting healthy eating in pregnant women [15]. This review will consider studies that evaluate diet and nutritional education programs, or training targeted for midwives and student midwives (hospital or community-based midwives, obstetric nurses, birth attendants, doulas, midwives alone or with other

health professionals) to provide healthy eating knowledge and advice for pregnant women. The education and training program proposed in this mixed-methods study will be a structured program therefore the considered studies in the review may have a defined period, facilitated as a workshop or seminar. The education and training program can be provided by any health care professionals such as dietitians, nutritionists, midwives, health educators, or any other accredited personnel. The primary outcomes of the systematic review are as follows: (1) level of knowledge acquired by midwives and student midwives regarding diet and nutritional requirements in pregnancy measured by any scale or questionnaire and (2) the level of confidence acquired by midwives and student midwives regarding diet and nutritional requirements in pregnancy measured by any scale or questionnaire.

The systematic review was conducted using a three-stage comprehensive search of seven electronic databases and grey literature. Two independent reviewers assessed each paper prior to inclusion using the standardized critical appraisal instruments for evidence of effectiveness developed by the Joanna Briggs Institute. Preliminary results from this systematic review provided guidance for the design of this mixed-methods study and the development of a semistructured questionnaire to be used at the three-time points during the study. The questionnaire will gather data to investigate midwives' level of knowledge and confidence to provide healthy eating education and support to pregnant women. The literature highlighted that there is a lack of studies exploring the role of midwives in antenatal nutritional health education [16-18]. The lack of evidence, therefore, justifies exploring the public health role of midwives to address the nutritional health education of pregnant women and their developing baby. Previous studies have shown that some midwives self-reported a lack of basic knowledge of nutrition requirements during pregnancy [16,17]. A cross-sectional study that investigated Australian midwives' nutrition knowledge, attitudes, and confidence to provide nutrition education during their undergraduate studies and after registration found that some midwives did not receive evidence-based nutritional health education [16]. It is, therefore, important to investigate the needs of midwives to improve the way in which nutritional health education is provided to pregnant women.

Aim and Objectives

This paper describes the study protocol for a healthy eating education program during pregnancy. The aim is to design and evaluate a healthy eating education program to enhance midwives' knowledge, understanding, and confidence to support South Australian pregnant women to eat healthily during and after their pregnancy. The study will address the following research objectives through two phases.

Phase 1 will assess midwives' knowledge and level of confidence when providing information on diet and nutrition education for pregnant women and evaluate a healthy eating education program.

Phase 2 will explore midwives' views on how they provide advice on healthy eating for pregnant women, through an individual interview after they have attended a healthy eating education program.

Methods

Study Design

This proposed research study protocol will utilize a sequential explanatory mixed-methods approach guided by a conceptual framework and undertaken in two phases, namely a quantitative phase (Phase 1), followed by a qualitative phase (Phase 2).

Conceptual Framework

The framework elements in this mixed-methods study are philosophical assumptions (pragmatic knowledge claims), strategies including Sequential Explanatory Mixed-Methods Design, and methods (to describe data collection procedures). These are summarized in Figure 1.

Philosophical Assumptions: Pragmatic Knowledge Claims

Pragmatism is considered as a worldview, which accepts multiple realities and supports practicality when addressing the research question and it reflects both biased and unbiased perspectives. This pragmatic perspective as a philosophical methodology draws on utilizing "what works," utilizing different aspects of this, setting priority to the value of the research problems and questions, and gathering both objective and subjective data [19].

Strategies Including Sequential Explanatory Mixed-Methods Design

This proposed research study will use a Sequential Explanatory Mixed-Methods Design according to Creswell [20]. The two phases will gather both quantitative and qualitative data in a sequential manner. The first phase involves collecting and analyzing quantitative descriptive (numeric) data, which gives a general picture and overview of the data related to the research problem. The second phase involves collecting and analyzing qualitative (text) data, which will help explain the general overview and explore the midwives' views in more depth. The interpretation of results is usually undertaken following completion of the second phase. Figure 2, adapted from Jirojwong, Johnson and Welch [21] and Creswell [20], describes this process. Finally, the data obtained from the two phases are integrated [22] to draw a comprehensive and accurate conclusion. The research outcomes using this approach provide a broader, more comprehensive picture of a specific phenomenon compared to using either a quantitative or qualitative method alone [23-25].

#### Methods of Data Collection

A semistructured questionnaire will be used in Phase 1 to collect data. The questionnaire was designed and adapted from the literature and previous applied questionnaires [16,18,26] to examine healthy eating and nutrition during pregnancy, as well as problems related to nutrition during pregnancy [17,27-41]. This questionnaire will be used to collect data at 3 time points.

Figure 1. Three framework elements of inquiry for a mixed-methods approach developed from Creswell [22].
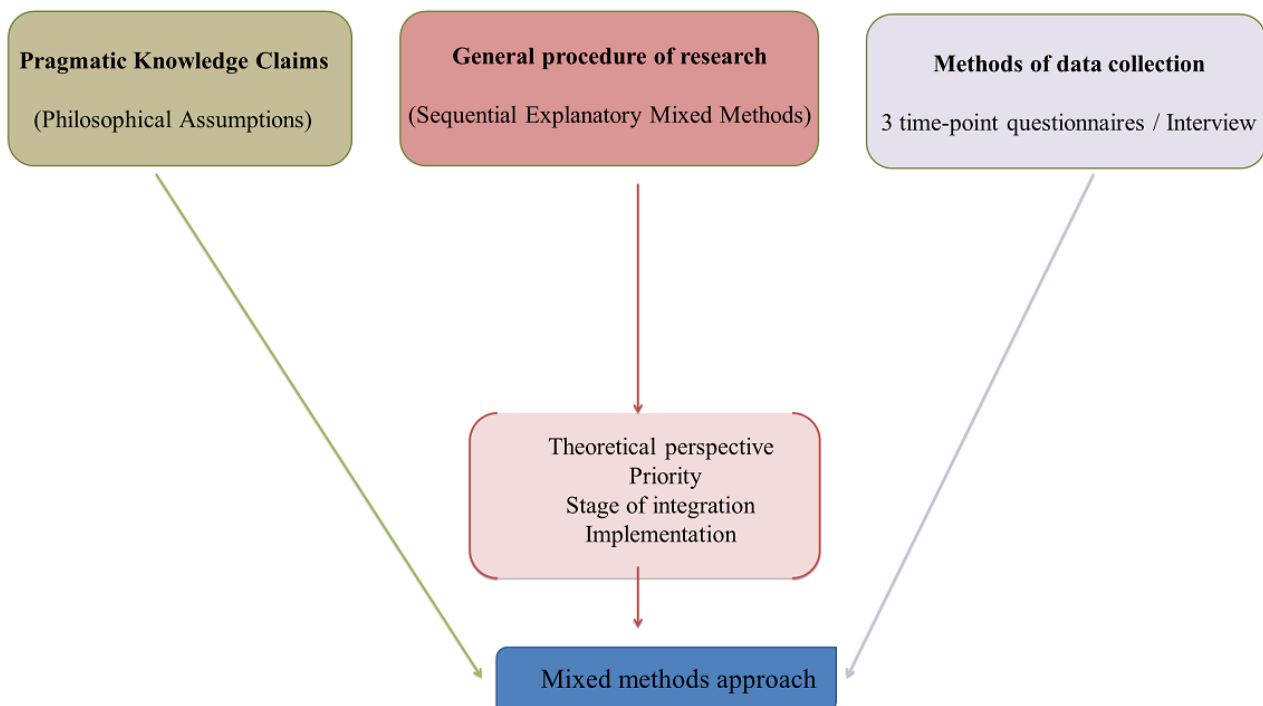
Figure 2. Sequential Explanatory Mixed-Methods Design adapted from Jirojwong, Johnson and Welch [21] and Creswell [20]. ANOVA: analysis of variance; QUAL: qualitative data; QUAN: quantitative data; SPSS: Statistical Package for Social Sciences.
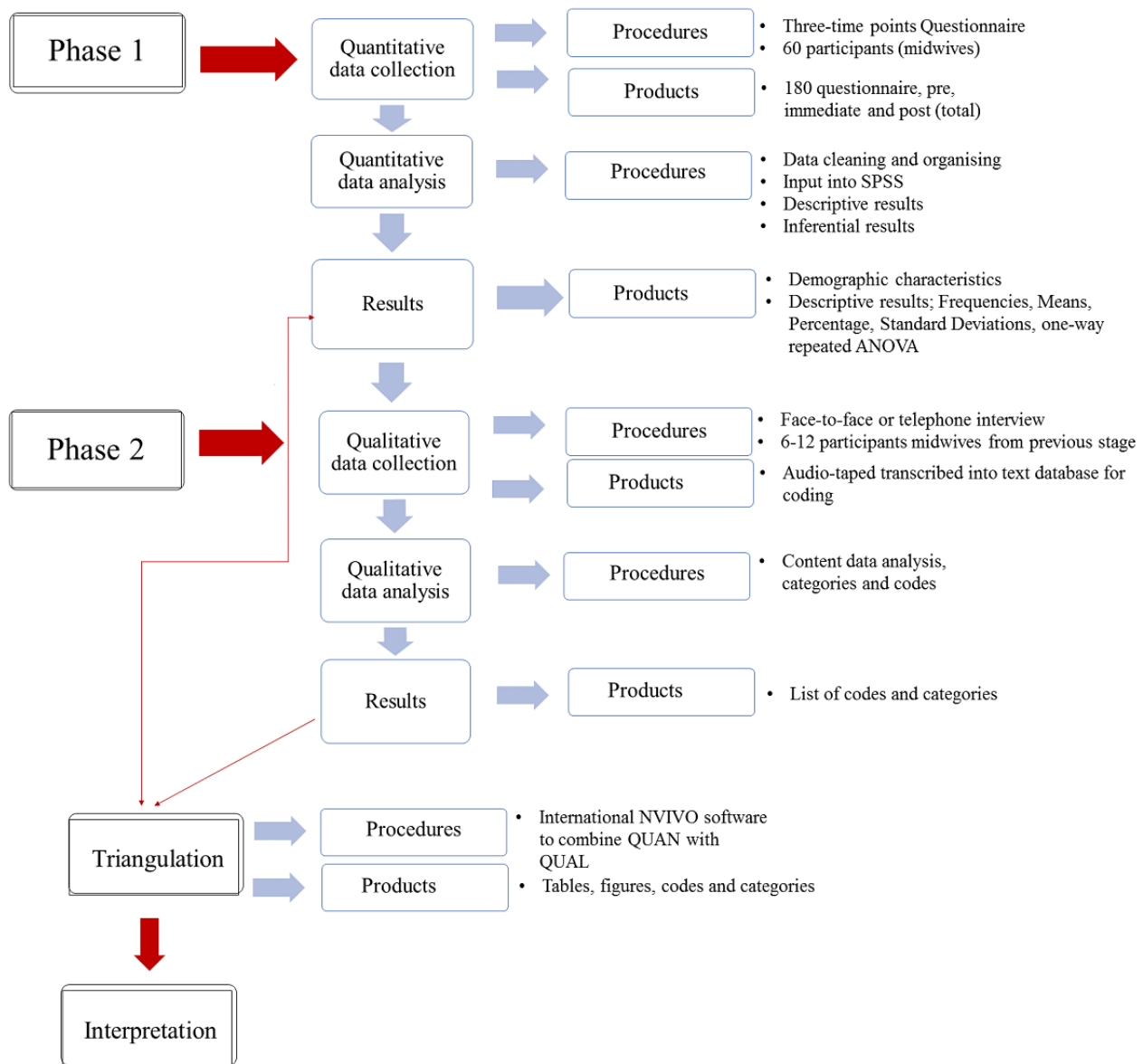
The semistructured, pre-educational questionnaire used in this study included 5 sections asking midwives for their previous nutrition education, level of confidence, nutrition knowledge, an invitation to attend the workshop or webinar, and demographic characteristics based on a previously validated questionnaire (used after seeking permission from the author) [16]. For the immediate- and post-educational questionnaires, midwives will only be asked about their level of confidence and nutrition knowledge.

A pilot of the questionnaire will be undertaken to ascertain validity and reliability of the instrument. Questionnaire validity refers to the extent to which it measures what the questionnaire is intended to measure. Measuring content validity assesses whether the instrument adequately covers all the content with respect to the variables and it is measured by asking experts (face validity testing) their opinion about whether an instrument

measures the concept intended [21,42]. The expert panel will be consulted and invited to comment on the questionnaire to give feedback on the instrument (ie, on wording and the order of the questions). Three midwifery experts and 2 dietitians will be invited to review the questionnaire and feedback will be obtained on the clarity of the instrument (questionnaire).

A common method used to estimate the reliability of a measurement is the "test-retest" method, which involves the same test being given to the same participants more than once under the same conditions to evaluate if the responses to the test reflect true variables [42,43]. This questionnaire will undergo a pilot using the "test-retest" method with the aim of assessing whether the same results will be obtained, and therefore its reliability. The pilot will involve three to five midwifery researchers and students who will be invited to participate in the pilot and will not be involved in the main

study. The midwifery researchers and students involved in the pilot will complete the pre-educational questionnaire twice, once immediately and then again one week later.

Phase 2 of this study will be initiated after the completion of Phase 1. It will consist of a semistructured face-to-face or telephone interview to be scheduled 8 weeks after attendance of the Healthy Eating Education Program. The designed interview schedule will be piloted with three to five midwives or student midwives, and any suggestions or recommendations obtained during the pilot will be incorporated into the final version of the interview schedule.

Phase 1 Methodology: Designing, Facilitating, and Evaluating the Healthy Eating Education Program

Designing the Workshop or Webinar

The workshop or webinar will be designed based on results gathered from the systematic review and utilize material from the "EatWell" Assist program [44] and will be designed based on the following criteria: (1) the healthy eating educational program will incorporate evidence-based guidelines and (2) explain the significant nutritional elements including sources, importance, and recommended intake or amount. Furthermore, a workbook will be designed for workshop activities and recommended reading.

Study Website

The study website will include detailed information about the study. The home page will introduce the study and clearly state its aim and objectives. Other webpages will provide information on how to participate in the study, the ethical considerations related to the study, the research team, and how to contact the primary researcher. Relevant webpages will give prospective participants the option of attending a workshop or webinar, provide online questionnaires to complete, and provide an invitation to attend a follow up face-to-face or telephone interview.

Recruitment

Midwives residing and employed in South Australia will be invited to participate in the study. An invitation will be sent via the Australian College of Midwives (ACM) and the Australian Nursing and Midwifery Federation (ANMF, South Australian Offices) e-bulletins. A dedicated study website will be designed and utilized with a domain name (http://healthyeating educationformidwives.com/) for midwives to access and participate in the study. An internet advertisement using Google search engine and social media outlets such as Facebook and Twitter will be linked to the study website. A study Facebook page and Twitter account will be set up to increase awareness of the study.

Pre-educational Workshop or webinar Questionnaire to Investigate Midwives' Knowledge and Level of Confidence Regarding Healthy Eating

A pre-educational healthy eating questionnaire will be undertaken to investigate the midwives pre-existing knowledge, understanding, and level of confidence prior to attending the healthy eating education program.

Settings

The setting for the participant workshop will be the University of South Australia, School of Nursing and Midwifery, City Campus, Adelaide, or other University of South Australia Campuses, such as Whyalla or Mount Gambier, if this is preferred. For participants who have a preference to attend online or are unable to attend a workshop, an online webinar will be offered.

Implementation of Healthy Eating Education Program

The healthy eating education program will be delivered by attendance at a workshop or webinar (online virtual classroom).

The first author, SO, will have cofacilitation support to introduce and facilitate a "Healthy Eating in Pregnancy" education program (workshop or webinar) for midwives. The workshop duration will be approximately two hours (including time for refreshment and completing the posttest educational questionnaire). The guide used for the contents covered in the workshop and webinar is described in Textbox 1.

Textbox 1. A guide for content to be covered in the Healthy Eating Education Program workshop or webinar.

- Healthy eating and dietary requirements

- Macronutrients (protein, carbohydrate, fibers, Omega 3 and fats and essential fatty acids), micronutrients (include vitamins A, C, E and B complex and minerals [Se, Fe, Ca, Mg, and Zn]), folic acid, fish consumption and iodine with pregnancy. The aim of this information is to improve the participant's knowledge about role and sources and how it can enhance health and reduce risk.

- Portion sizes

- Eating myths

- Vegetarians and vegans eating

- Cultural food choices

- Eating habits and behaviors

- Preparing food and hygiene safety

- Physical activity

- Dental care during pregnancy

- Probiotics and prebiotics

The teaching materials will include a workbook, quiz, brochure, and recommended reading.

Posteducational Workshop and Webinar Questionnaire

The same pre-educational questionnaire administered to the midwives prior to attendance of the workshop or webinar will be completed again at the end of the workshop or webinar to evaluate the midwives' healthy eating knowledge immediately after the education program. This questionnaire will be provided in a PDF format (for the workshop) and online via the study website for the webinar (virtual classroom), according to the midwives' preference. The researcher and workshop facilitator will remind the midwives that they will be contacted in six to eight weeks after attending the educational program to complete a final questionnaire (using the same pre-educational questionnaire).

Follow-up Educational Workshop or Webinar Questionnaire

Six to eight weeks after attending the workshop or webinar, the primary researcher will contact the midwives by telephone or email and ask them to complete the final posteducational questionnaire.

Participants or Population

Midwives residing and employed in South Australia who are members of the ACM and ANMF will be invited to participate in the study. Australian social media groups such as the ACM and ANMF groups on Facebook and Twitter will be provided with a link to the study website.

Sample Size and Power Calculation

A single-factor, repeated measures design with a sample of 5 subjects, measured at 3 time points, achieves a 91% power to detect differences among the means using a Geisser-Greenhouse Corrected F Test at a .05 significance level. The SD across subjects at the same time point is assumed to be 25. The pattern of the covariance matrix is to have all correlations equal with a correlation of .70 between the first and second time point measurements. The SD of the hypothesized means is 17.00. The expected mean scores over the 3 time points are 50, 90 and 80.

Based on a power calculation, only a very small number of midwives (n=5) would be required to demonstrate the expected large increase in knowledge and level of confidence as a result of the healthy eating education program (workshop or webinar). However, we will recruit a larger number of participants (n=60) to ensure that we have midwives covering abroad range of age, experiences, and locations.

Data Analysis

Data from the pre-educational questionnaire will be entered into the Statistical Package for Social Sciences (SPSS) IBM version 25. Descriptive analysis will be used to examine the midwives' demographic characteristics, such as age, level of education, years of experience, type of maternity services, previous education related to nutrition, and place of practice. The results will be used to describe and summarize the data collected. Data will be presented as frequencies, means, SDs, and percentages. Data related to the level of knowledge and confidence will be analyzed using mixed-effect models to examine the variance in nutritional knowledge and level of confidence over the 3 time points.

Descriptive analysis of questionnaire data will be carried out using an ordinal (1-5 point) Likert scale with the range from 'very confident' (5) to 'not confident at all' (1). Spearman's rank correlations coefficient will be used to evaluate the strength and relationship between two or more variables. Inferential statistics used for making conclusions will compare differences and associations using analysis of variance (ANOVA) tests [25]. Open-ended question responses will be coded as positive or negative, and for content analysis to compare different categories at different time periods [45]. A bio-statistician will be available to assist with the analysis. All questionnaire responses will be numerically coded using a predefined coding scheme.

Phase 2 Methodology: Exploration of Midwives' Views of the Healthy Eating Education Program

Eight weeks after the Healthy Eating Education Program, a small sample of midwives who participated in the program (12 or less) will be invited to participate in a semi-structured interview either conducted face-to-face or by telephone. An interview schedule will guide the interviews, which will take approximately 30-60 minutes and obtain the participants' views on the healthy eating education they received. The semi-structured interview will help the midwives to express their feelings freely and enable the researcher to encourage midwives to expand more on what is being discussed. However, the researchers will need to remain objective and open to the possibility that the data may be different than expected [25]. The interview guide will be developed from the results of the systematic review (included studies) and findings of Phase 1.

Selection of Participants for Phase 2

A purposive sample of midwives (approximately 12 or less) will be interviewed 8 weeks after completing the Healthy Eating program. Data from participants' interviews will be recorded and transcribed verbatim. The transcripts will be analyzed on an individual basis until data saturation is reached and recruitment will then cease. The selection of midwives will be based on midwives who work in urban and rural (South Australia) antenatal clinics, Midwifery Group Practices and antenatal parent education classes.

Data Analysis in Qualitative Research

Content analysis will be used to evaluate the semistructured interview responses. This method is used for identifying, analyzing, and reporting concepts or categories within data. This analysis method minimally organizes and describes data sets in detail. Content analysis as a research strategy is a methodical and systematic method for describing and evaluating phenomena, which allows for testing theoretical issues to establish understanding of data and comprehension of information [46,47]. The aim of utilizing content analysis will be to achieve a broad description of midwives' views after receiving the healthy eating education.

Content Analysis Process

Interview content analysis will be based on the Conventional content analysis approach which will assist to gain more insights on healthy eating in pregnancy education for midwives after they have received the training [48]. The 3-phase framework for content analysis as described by Elo and Kyngas [45] will be utilized as described below.

Preparation Phase

This phase commences with selecting the unit of analysis, this unit can be a word or a theme, relevant to the research question. Using the manifest content where the researcher describes what information was actually said (ie, uses the same words and describes the visible and what is said in the text) [49].

Organizing Phase

After making sense of the data, an inductive approach will be used starting from open coding for whole reading of the dataset, creating grouping and categories, then abstraction to formulate a general description of the research topic through generating main categories, generic categories, and subcategories from analyzed data.

Reporting the Analyzing Process and the Results

A final report will be written to provide brief, classified, logical, varied, realistic, and interesting conclusions from the story obtained from the data obtained, within, and across, all codes and categories.

Results

Triangulation of Quantitative and Qualitative Data Findings

The sequential explanatory design enables the reporting of participants' cases as one continued story starting from the pre-educational questionnaire, then the healthy eating education workshop or webinar, continued to the participants attending an interview based on the findings from the systematic review and finally to make general conclusions about the participants' knowledge, level of confidence views, and understanding their role in healthy eating education. According to the conceptual framework (Figure 1) and the sequential explanatory design discussed in Figure 2, an initial data analysis will be undertaken when completing the systematic review. Moreover, this analysis will continue during Phase 1 (quantitative data extracted from questionnaires with closed- and open-ended questions). The results of the systematic review and the quantitative phase will help to develop a guide for the semi-structured, in-depth interviews with midwives. Semi-structured interview data will be analyzed using content analysis, and the results outcome from this phase will be integrated together with the previous analysis to obtain a broader and more accurate picture describing midwives' nutritional knowledge and confidence.

Ethical Considerations

Ethics approval has been granted from the Human Research Ethics Committee at the University of South Australia. Approval has been given to advertise the study via the ACM and the ANMF professional bodies to invite midwives to participate in the study. The program will also be recognized by the ACM for continual professional development points. The link to the study website will be included. The study website will also be linked to the Australian Midwives social media groups such as the ACM and ANMF groups on Facebook and Twitter. To maintain confidentiality, a unique identifying number (participant ID) will be assigned to the data collected for each participant. Participation in the study is voluntary and contact details of the research team and a person who is responsible for receiving any complaints will be provided on the study website.

Participants will be able to access a participant information sheet that will outline the purpose of the study, the phases and its importance, via the study website. Participation is voluntary, and midwives can withdraw at any time without influencing their status now or in the future. The participants will be informed about the upcoming workshops and interviews if they wish to participate, and interviews will be audiotaped for further analysis. The transcripts and tape will be securely stored in a locked cabinet in a locked room and only the research team will have access to it.

The results will be nonidentifiable, and findings will be published in journals and at conferences. Participants will be able to access a summary of the findings from the study website. Anticipated benefits of the study include an increase in the level of knowledge for midwives regarding nutritional healthy eating education. Midwives who participate in the health education program (workshop or webinar) will be given two points of Continuing Professional Development on completing the education program through the ACM.

Discussion

Study Rationale

It is anticipated that there will be several expected benefits from undertaking and participating in this proposed research. For example, midwives who reside in South Australia will have an opportunity to attend a healthy eating education program (either as a workshop facilitated on campus at the University of South Australia and also accessible as an internet-based webinar) which will be freely available to access and be validated through this research study. This healthy eating educational opportunity has the potential to enhance the knowledge and confidence of midwives who reside in South Australia. It is envisaged that participation in this study will improve midwives' awareness and knowledge of evidence-based guidelines regarding healthy eating in pregnancy. In addition, midwives' confidence may increase to enable them to provide additional nutritional healthy eating education and support for pregnant women. Should this program increase the midwives' knowledge and confidence to educate women, this may improve maternal and fetal outcomes.

Conclusion

The preliminary results of the on-going systematic review suggest that there is clear justification to undertake this mixed-methods study to investigate and explore midwives' knowledge, understanding and confidence to support pregnant women to eat healthily. Findings and conclusions from this systematic review has provided some guidance for the design

and development of this protocol. The questionnaire has been designed to be used at 3 time points during the first phase of this research study. A follow up second phase will provide an opportunity to gain a more in-depth understanding of midwives' views after they have received the healthy eating education program. The results from both phases (quantitative and qualitative) data sources will help to draw conclusions to address the research topic.

Acknowledgments

Authors' Contributions

All authors listed have contributed sufficiently to the development of ideas and the writing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report.

[PDF File (Adobe PDF File), 335KB - resprot_v7i5e143_app1.pdf]

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Abbreviations

ACM: Australian College of Midwives
ANMF: Australian Nursing and Midwifery Federation
ANOVA: analysis of variance
SPSS: Statistical Package for Social Sciences

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Protocol

Cocreated Smartphone App to Improve the Quality of Life of Adolescents and Young Adults with Cancer (Kræftværket): Protocol for a Quantitative and Qualitative Evaluation

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Abstract

Background: Adolescents and young adults with cancer face significant challenges during the course of their medical treatment and recovery from illness. Many adolescents and young adults struggle with long-term complications in the physical, psychosocial, economic, and academic domains. Mobile health (mHealth) interventions provide an innovative platform for delivering supportive care, particularly through the utilization of apps on smartphones and tablets. To create a successful mHealth intervention for adolescents and young adults, youth input and feedback is essential. The process of cocreation, in which the target app user has a direct role in dictating design and function, was utilized to create the prototype smartphone app for adolescents and young adults with cancer, "Kræftværket."

Objective: The objective of this paper is to describe the protocol for the evaluation of the Kræftværket app, a prototype app designed via cocreation, to support and improve health-related quality of life for adolescents and young adults with cancer.

Methods: The Kræftværket app has three primary features, (1) a symptom and activity diary, (2) a supportive communication network between app users, and (3) a "one-stop shop" information bank with practical information as well as links to patient organizations and other resources. The app will be evaluated in two phases, a pilot test and an implementation test. In the pilot test, the app will be launched to a test group of 20 adolescents and young adults aged 15 to 29 years, selected for equal representation amongst age group and treatment status. Patients will be allowed to utilize the app over the course of six weeks and will complete a baseline and follow-up European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) health-related quality of life inventory. In addition, participant focus group interviews will be conducted according to a semistructured interview guide. Resulting data will be analyzed using thematic analysis. Results and appropriate analysis from both the qualitative and quantitative branches of the pilot test will be discussed amongst the research group, and appropriate changes based on user feedback will be made to the app before the final project phase. In the implementation test, the app will be provided and utilized by a sample of 50 adolescents and young adults aged 15-29 years selected for equal representation amongst gender, age group, diagnosis, and treatment status over the course of 3 months. Participants will be asked to complete a baseline and follow-up EORTC QLQ-C30 HRQoL inventory.

Results: Pilot testing is expected to take place in February 2018, and implementation testing is expected to begin May 2018.

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Conclusions: It is the hope that Kræftværket app will serve as a beneficial and easily utilized product. The process of evaluating the app and its effect on quality of life will address the absence of evidence-based mHealth interventions, and attempt to validate new approaches to benefitting adolescents and young adult oncology patients in the digital world.

Registered Report Identifier: RR1-10.2196/10098

Introduction

Adolescents and young adults (AYAs) are a group with health care needs which are separate from both adult medicine and pediatrics. Patients in this age group present unique and significant physical, psychological, and cognitive challenges through hospitalization and beyond, which have often been overlooked, particularly in the fields of hematology and oncology [1-5]. AYAs with cancer report a decrease in health-related quality of life (HRQoL), regardless of other demographic factors such as gender, age, or ethnicity [6,7] and struggle with long-term complications in the physical, psychosocial, economic, and academic domains as a consequence of their disease and recovery process [8-10].

While the age range definition for AYA patients varies by organization, the Danish Cancer Society has compiled a large-scale report addressing the AYA oncology population aged 15 to 29 years [5]. This age range is used at our institution, as opposed to those proposed by the WHO (ages 12-24 years) or US National Cancer Institute (ages 15-39 years), in order to complement existing literature on AYA hematology and oncology in Denmark, as well as to correspond with the age range provided for AYA support organizations in Denmark [5,11,12]. Within this age range, approximately 500 AYAs in Denmark are diagnosed with cancer each year [5,13]. While this is a small number of patients, conducting AYA cancer research in Denmark is convenient due to a highly accessible cancer registry and the elimination of certain variables which could influence cancer research, such as health care insurance status, due to the presence of a nationalized health care system [14,15].

Technology provides a contemporary method of delivering health interventions, particularly to AYA patients. Many interventions have previously been designed specifically for AYA cancer patients and contain tools to assist with symptom tracking, health promotion, and social networking [16,17]. Mobile health (mHealth) apps are commonly used to design health interventions and can be highly beneficial due to their ability to portably connect patients to peers, health care teams, and validated sources of information, as well as to complement existing technologies such as Web-based interventions or health tracking devices. These apps can be used on tablets or smartphones, where the term "smartphone" is defined as a mobile phone with additional functionalities, such as internet access and has an operating system capable of downloading and running such apps. Such apps have various purposes, including, but not limited to, social networking, health tracking, health promotion, and provision of information [18,19]. The current availability of mHealth apps for AYAs with cancer is widespread, however, there are limitations to both the content and validity of these apps. Very few apps have been developed with a defined protocol involving both health care professionals and AYAs, and even fewer have demonstrated their effectiveness and benefit to the population [19-21]. It is possible, however, that these tools may harbor potential for improvement of HRQoL in AYA cancer patients.

Additionally, mHealth apps could be of value due to their perceived ability to positively influence self-efficacy, empowerment, and self-management capabilities of patients [22]. Bandura et al have described the theory of self-efficacy, defining self-efficacy as people's beliefs about their ability to influence change throughout their lives [23]. Frequently, self-efficacy is described in coordination with empowerment, linking the individual's personal abilities with greater structures in political and social domains [24,25]. High levels of self-efficacy and empowerment provide individuals a sense of personal agency and ability to exercise control of their surroundings [23-28]. This may be reflected in improved abilities of self-management, or an individual's ability to manage the consequences of living with disease on a physical, social, and psychological level [25-29].

Therefore, in order to create a successful mHealth intervention, the input of AYAs themselves is critical to both the design and evaluation of such interventions. Many existing technologies intended for patient use are not developed or evaluated based on user perspectives and, as such, not all existing mHealth interventions intended for AYAs are user-friendly or adequately meet the needs of their target populations [20,21,30,31]. AYA populations are frequent consumers of mobile technology and would therefore benefit from technology resources developed with their perspective [5,32-34].

At a technology intervention idea workshop, AYAs were asked to discuss their life with cancer, identify challenges they faced, and then discuss a plan for a technology-based intervention to address these needs. The perspective of both AYAs currently receiving treatment for cancer and survivors in remission was requested. At the end of the workshop, the participants concluded that a smartphone app would be an effective tool for empowering AYAs and improving their HRQoL [35]. Based on this idea, funding was raised and the process of cocreating an app, involving AYAs with cancer, was initiated to develop a prototype for a user-friendly smartphone app. The current app prototype has been designed to serve as a support tool for AYAs, integrating community support features, symptom tracking, and

a "one-stop shop" information database into one's pocket for maximal convenience and benefit as a cancer patient or survivor.

Based upon the background of mHealth interventions for AYAs and our developed app prototype, the objective of this article is to describe the protocol for the evaluation of the Kræftværket app, a smartphone app designed via cocreation for AYAs with cancer.

Methods

Participants and Recruitment

Kræftværket is a youth support center and social organization for AYAs with cancer aged 15 to 29 years at Rigshospitalet in Copenhagen, Denmark [36]. The name of both this center and the smartphone app described in this project, Kræftværket, is composed of the Danish words for "power plant" (Kraftværk) and "cancer" (Kræft), evoking empowerment throughout the time of cancer treatment and recovery. Throughout all phases of the project, patients will be recruited from a population of AYAs who are currently receiving or have received treatment at Rigshospitalet for cancer. Participants will be invited to participate in the study by a youth coordinator either by physical meeting or via the closed Kræftværket Facebook group. The youth coordinator will explain participation details and the risks and benefits of participation. Eligible participants who are already part of the closed Facebook group will be provided these details via a personal message. Eligible participants who are not already part of the Facebook group will be invited to join but will not be required to do so.

Inclusion criteria from this population will be AYAs aged 15 to 29 years with access to smartphones and the internet, including cellular data or Wi-Fi. Exclusion criteria will be those with an inability to read and write in Danish. Recruitment will be targeted to include a broad range of participants across the AYA spectrum with diversity in age (groups of participants aged 15-22 years or ≥23 years), gender, diagnosis, and treatment status (receiving active treatment or not receiving active treatment). Throughout phases II and III, participants that represent these demographics will be approached and targeted. Targeted recruitment for participants in Phase II will be based on age group and recruitment status, while in Phase III targeted recruitment will be based on gender, age group, treatment status and diagnosis. Sample sizes for phase II and III were determined based on prior research from other mHealth interventions [37,38].

Primary Intervention and Kræftværket App Features

The primary intervention is the smartphone app Kræftværket (named after the aforementioned youth sanctuary at Rigshospitalet), a comprehensive smartphone app designed for AYAs with cancer and AYA cancer survivors. After the research team performed a primary review of the literature, an idea generation workshop was performed in coordination with 12 AYAs attending Kræftværket to identify, create, and evaluate a single technology intervention that could increase self-empowerment and improve quality of life (QoL) in AYAs with cancer. This workshop confirmed that a smartphone app was an appropriate tool for intervention. The technology intervention workshop was initiated and run by the Kræftværket research group and it was specific for the population of AYAs with cancer. A cocreation project was initiated to develop the smartphone app designed from the input of AYAs. The initial workshop and all subsequent workshops were held outside of the hospital and were run by members of the research team or representatives from the partnering technology developer. Further project details, explanation of the cocreation process, and details about the app prototype are provided in a separate paper [39]. Phases II and III will evaluate the design model, allowing for changes based on the obtained results and feedback (Figure 1).

Cocreation is one method of tool development with patient and public involvement (PPI). PPI is believed to increase both the quality and relevance of a given product to its target population in terms of research objectives and outcomes [40]. As such, PPI is of frequent interest in social science and health care research.

Figure 1. Framework for development of Kræftværket smartphone app and evaluation of study design. EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of life Questionnaire Core 30.
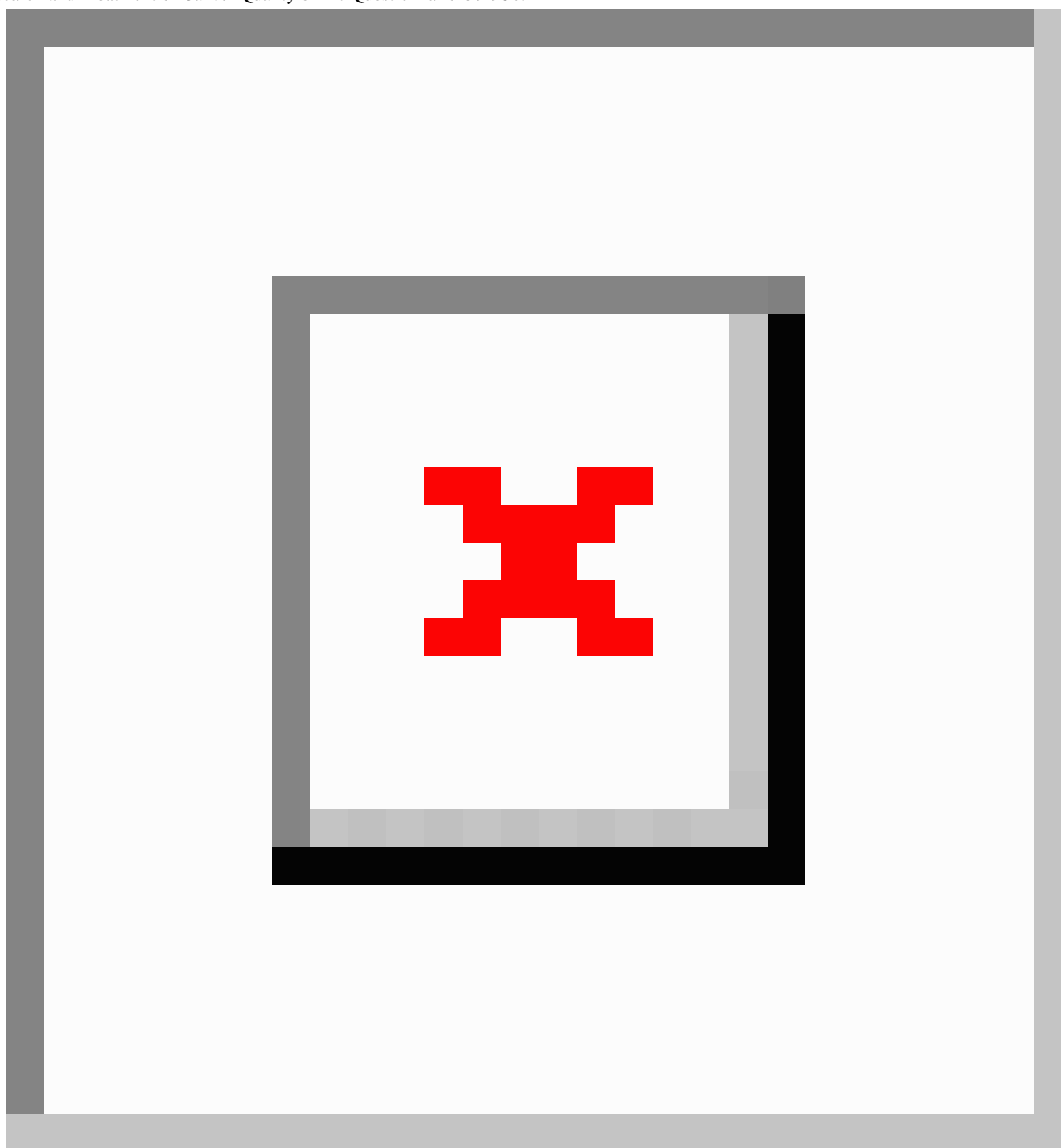
Cocreation is a process that allows the individuals who will utilize a product to have an active voice in its development, therefore shifting the focus and involvement away from professional stakeholders (such as health care professionals and the research team), toward those who would use the final product [39]. The process of cocreation was specifically selected to create a user-friendly app that will be beneficial and enjoyable for the target patient population [31,32,41]. During each workshop, the goals for the app were prioritized based on the AYA patients' specifications. After different concepts were developed, feedback was requested from the AYAs and the feedback was then integrated into the app. This process continued iteratively, where feedback would again be requested

and integrated into the app, and this process would continue until majority agreement was achieved on the final product. The app prototype was finalized after a series of three cocreation workshops with the input of 17 AYAs in total [39].

The Kræftværket app is a tool designed to be utilized both during and after cancer treatment and will be available on both iOS and Android platforms. Initial feedback from AYA patients at the first cocreation workshop identified three essential features of the smartphone app (Figure 2). These included (1) a diary which allows AYAs to track how disease and treatment may affect their daily life and mood which will be demonstrated visually as an insight-graph for patients to track their physical, mental, and emotional status; (2) a communication network

between app users to share knowledge and support with one another at any time, in the form of direct messaging and a public forum and (3) a "one-stop shop" information bank, where AYAs can access practical information, useful references, and links to patient organizations and other resources. The specific features of the Kræftværket app are presented in Textbox 1. Further details of the cocreation process, as well as its utilization in the development of Kræftværket app, and the app prototype's features are described in greater detail in a separate publication [39].

The functional prototype of the Kræftværket app will be launched in February 2018 for analysis in Phases II and III of the mHealth intervention project. Table 1 presents an overview of the target participants, data collection and analysis methods for phases II and III.

Both the proposed development and analysis of the Kræftværket app are intended to follow the Model for Assessment of Telemedicine Applications (MAST) framework for assessing the effectiveness and contribution quality of telemedicine apps based on scientific data. The MAST framework defines a 3-level approach to evaluating eHealth interventions addressing: (1) preceding considerations for intervention purpose and specificities, (2) assessments within 7 domains (the health problem and characteristic of the app, safety, clinical effectiveness, patient perspectives, economic aspects, organizational aspects, and sociocultural, ethical, and legal

aspects), and (3) transferability of the intervention to areas of expansion [42,43]. Table 2 summarizes specific outcome measurement goals and considerations taken during the development process of Kræftværket in relation to the MAST framework.

Phase II: Pilot Testing

The app will be launched to a test group of 20 AYAs. In the test group, 10 patients will be currently receiving treatment and 10 patients will have completed cancer treatment. Recruitment in both patient groups will be targeted for an appropriate representation of gender and age groups across the AYA spectrum (ages 15-22 and 23-29 years). During the pilot test, patients will utilize the app over the course of 6 weeks. During both phases II and III, patients will not be given any specific instructions on the frequency that they should use the app. They will be instructed to use the app as they see fit. Patients will provide baseline measurements of QoL using the European Organization for Research and Treatment of Cancer Quality of life Questionnaire Core 30 (EORTC QLQ-C30), a validated, internationally recognized tool for scoring quality of life among cancer patients [44]. At this time, HRQoL is the only outcome investigated by this protocol. No other EORTC tools or modules will be used in this protocol. At the end of the 6-week period, the participants will be prompted to complete the EORTC QLQ-C30 via the app. Quantitative EORTC QLQ-C30 data will be analyzed using one-way analysis of variance (ANOVA) test.

Figure 2. Screenshots of current development model for Kræftværket app.
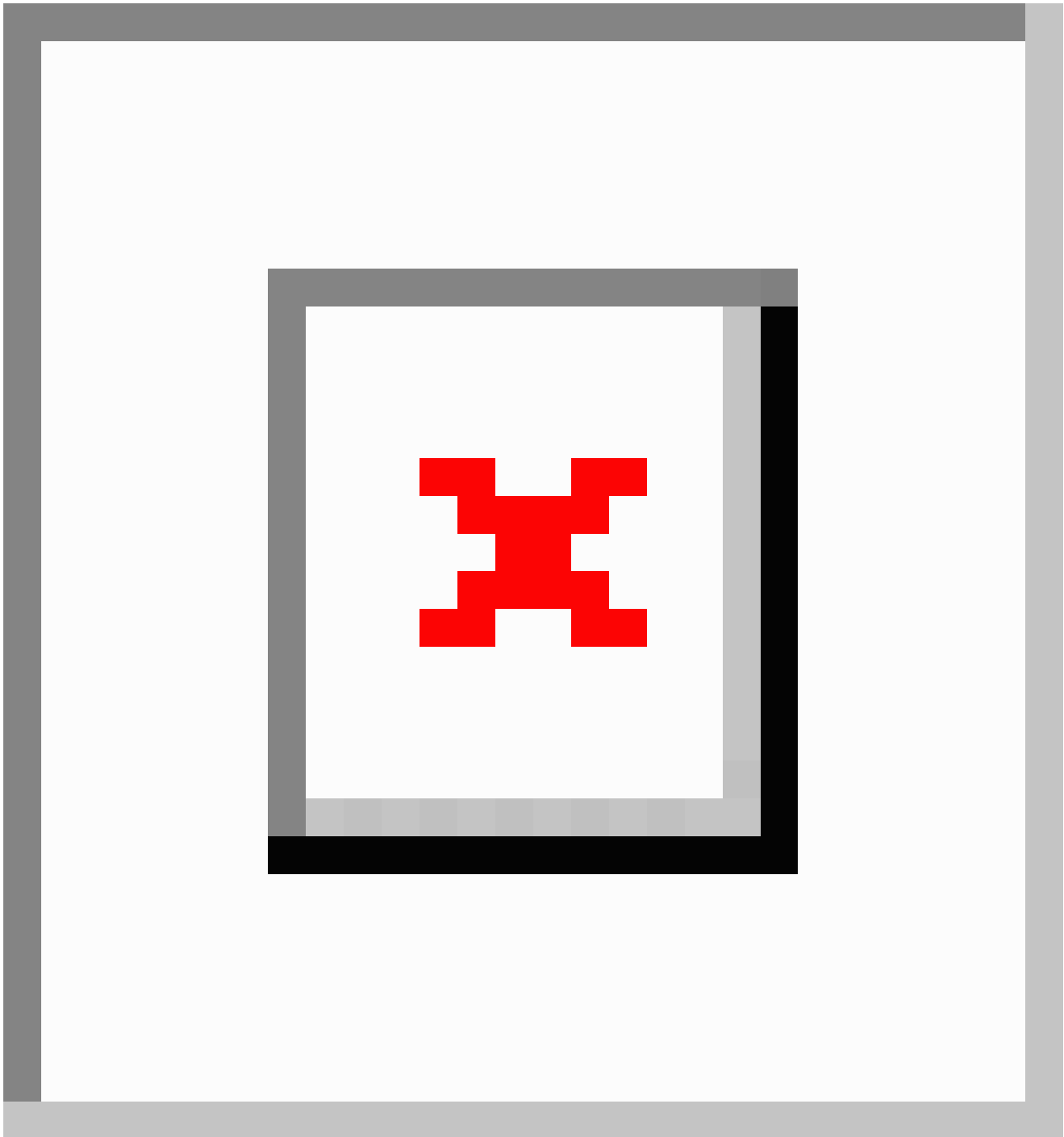
Textbox 1. Description of Kræftværket app features. AYA: Adolescents and young adults.

Symptom and Activity Diary

- Customizable diary to track and rate symptoms and wellness on a 5-point visual scale.

- Diary includes suggested tracking metrics, such as energy, nausea, or pain, as well as ability for users to add desired personal metrics.

- Checkboxes are included for daily activities, such as taking medication, meditating, or exercising.

- Ability to view prior entries on a 1-week, 1-month, or 3-month timeline and toggle metrics to view metrics altogether, or separately.

Communication Network and Forum

- Community forum for registered app users to post and share ideas and photos with other users under specific grouped topics.

- Anonymous posting feature.

- Private messaging function.

Information Bank

- Verified AYA-specific information from Danish Cancer Society.

- Videos featuring AYA cancer patients and survivors giving testimony on personal experience.

- Outgoing links from app to other patient support organizations and resources.

- Link to YouTube channel for uploading personal videos and testimony.

Table 1. Overview of Phase II and Phase III participants, data collection methods, and data analysis methods. ANOVA: analysis of variance; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of life Questionnaire Core 30.

Project Phase	Data Collection	Data Analysis
Phase II: Pilot Testing, N=20		
Quantitative	EORTC QLQ-C30	ANOVA
Qualitative	Focus group interviews; think-aloud Test	Thematic analysis
Phase III: Implementation Testing, N=50		
Quantitative	EORTC QLQ-C30	ANOVA
Qualitative	Additional focus group interviews if needed	Thematic analysis if needed

Table 2. Specific development strategies and outcome measurements used to address select domains from the Model for Assessment of Telemedicine Applications (MAST) framework. AYA: adolescent and young adult; mHealth: mobile health; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of life Questionnaire Core 30.

Preceding Considerations	Challenges and required resources specified by AYAs[a] with cancer that may be addressed by a supportive mHealth[b] intervention
Assessments within Seven Domains (project measurements and considerations)	
Health problem and app characteristic	Quality of life in AYAs with cancer and cocreated app specifically oriented to this patient population
Safety	Patient identifying information and data security according to Danish data regulation
Clinical Effectiveness	EORTC QLQ-C30[c]
Patient Perspectives	Qualitative interviews and cocreation app development
Economic Aspects	Continuous funding for app maintenance
Organizational Aspects	App ownership (determining role of developer and hospital)
Sociocultural, Legal, and Ethical Aspects	Data ownership and protection and informed consent of project participants
Transferability of the intervention to areas of expansion	Extension of the cocreation process may be useful for the development of future mHealth interventions. Further evaluation of transferability and areas of expansion will be discussed in future publications

In addition, participants will be asked to evaluate the app in two ways, first individually via a "Think Aloud" test and, secondly, by focus group interviews (asking questions about the cancer needs of the individual). Both the Think Aloud test and focus

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group interviews will be conducted on the same day in the Kræftværket day room. Participants will be asked to schedule their date for the Think Aloud test and focus group interviews during the informed consent process. The Think Aloud test and focus group interviews will be scheduled within two weeks of the 6-week app utilization period. All Think Aloud tests and focus group interviews will be performed with respect to the needs and physical condition of AYAs included in the study.

The "Think Aloud" method will be used to test the app's functionalities, as the patient is encouraged to verbally express likes, dislikes, comments, and concerns regarding the use the app [45]. This method of evaluating usability was selected as it provides both insight into the straightforward utilization of the app, as well as the user's personal insight and opinion of app utilization [45,46]. By using the Think Aloud test, it is possible to follow the decision-making processes of app users to understand which features are seen as useful or not useful, what questions arise and what aspects of the app are or are not intuitive [46]. The Think Aloud test will be performed by the app developer.

Focus group interviews will also be utilized to evaluate the performance of the app. Participants will be interviewed about their general perception of the app, as well as how the app relates to the following topics: everyday life, community and loneliness, information resources, symptoms, existential and identity issues, and empowerment. These focus groups will be conducted by an external researcher experienced in qualitative research, according to a semistructured interview guide. Focus group interviews will be recorded, transcribed verbatim, and analyzed for content using thematic analysis [47].

Results and appropriate analysis from both the qualitative and quantitative branches of the pilot test will be discussed amongst the research group, and appropriate changes based on user feedback will be made to the app before the final project phase.

Phase III: Implementation Testing and Quality of Life Evaluation

In the final phase, the app will be provided and utilized over 3 months by a sample of 50 AYAs aged 15-29 years whose treatment is either in progress or completed. Participants will complete the EORTC QLQ-C30 at baseline (before utilization of the app), and then repeat the EORTC QLQ-C30 via the app, after prompting, at the end of the three-month period. Quantitative data will be analyzed using one-way ANOVA test.

If a need for further qualitative analysis is identified during Phase II, additional focus group qualitative interviews using a semistructured interview guide will be performed during Phase III on an as-needed basis. If additional focus group interviews are performed, these interviews will be recorded, transcribed verbatim, and analyzed for content using Thematic Analysis [47].

Ethical Considerations

All identifying patient information will be anonymized. Data collected from the app, including app usage and content, will only be evaluated as a whole. As such, no data within the app will be able to be seen or identified from a specific individual.

All participants will sign informed consent forms prior to participation in any study procedure. If a participant is under the age of 18, caregiver informed consent will additionally be obtained. The study has been submitted to the Danish Data Protection Agency. This protocol is to be performed in accordance with the ethical recommendations of the Helsinki declaration. Patient confidentiality will be assured, and in future publications no identifying patient information will be utilized. Alphanumeric codes will be used throughout data analysis to anonymize patients. No identifying patient information, such as name or birthdate, will be used when discussing qualitative or quantitative data. Ethical approval of qualitative studies by the regional ethics committee is not necessary in Denmark.

Results

The development and trial of the Kræftværket app received funding February 2017 from Trygfonden, a non-profit foundation. At the time of this paper's submission, participants had completed 3 app development workshops and 3 ad hoc meetings between September 2016 through August 2017, and the Kræftværket app was in the final stages of visual design and programming for iOS and Android. Pilot testing and initial QoL-research will take place in February 2018, and implementation and extended QoL testing is expected to begin May 2018.

Discussion

Principal Findings

This paper outlines a protocol for the evaluation of a user cocreated smartphone app for AYAs with cancer. While many mHealth apps exist, few have been thoroughly investigated to determine their efficacy and benefit [20] and this is particularly true for AYAs with cancer. In literature to date, there is a significant absence of apps that have been thoroughly evaluated [21,32]. It is the goal of the research team behind this protocol to address this absence with our evaluation of Kræftværket app.

Smartphone app interventions have great potential to benefit AYA oncology patients through increased access to information, symptom and status tracking, and supportive social networking. In prior studies, a lower HRQoL was associated with decreased autonomy, social support, coping abilities, and unmet information needs among AYA patients with cancer [25,48-50]. However, literature reviews focusing on HRQoL have also indicated that increased social support—such as that from family, friends, or other cancer survivors—can improve HRQoL to benefit patient outcomes [6]. Social support from other cancer survivors has been previously noted as particularly helpful in improving HRQoL [25,50,51]. Other app features such as symptom tracking diaries and similar tools also show promise in supporting AYA app users and have been reported as helpful and easy to adhere to [52]. Lastly, meeting information needs with AYA-associated resources are frequently attributed to changes in HRQoL [6,48,53] As such, the inclusion of an information database featuring verified information in a youth-friendly format is another valuable feature.

It can be hypothesized that the provision of disease and personal self-management via tracking, a supportive social system, and the availability of information will benefit HRQoL. The utilization of an app platform will add an additional level of benefit—as a mHealth intervention will allow the utilization of support resources regardless of geographic location or time [18,19].

Limitations

This project could be limited by the population size of AYA oncology patients in Denmark, approximately 500 per year [5]. On the other hand, Denmark makes an excellent model country due to a nationalized registry of cancer patients, as well as a nationalized health care system that alleviates pre-existing burdens due to insurance and welfare systems [14,15]. It is the authors' expectation that the results of a Danish study can provide a model situation for the development of an app for young people, and that the results and findings from this project can then be utilized in the development of future apps outside of Denmark, helping AYAs both on a national and international scale.

A second limitation of the project is the timeline. Phase III will occur over a period of 3 months. However, pending the resources attached to our current project, we believe that 3 months will be sufficient to complete pilot testing, analyze data, and make changes to the app in response to pilot participants' feedback. Longer term follow-up is not proposed in the current timeline due to funding limitations but may be pursued at a later time. Furthermore, it will be difficult to determine whether or not the app will continue to be utilized longer-term by AYA cancer survivors after the immediate time of their illness and recovery. Further studies should be performed to determine the utilization of an app for AYA cancer patients and survivors beyond the course of three months.

Conclusion

Many apps have attempted to address the needs of AYAs with cancer, but there are few apps that have been reviewed to a sufficient standard of scientific merit. The Kræftværket app's analysis protocol aims to address this. The process of evaluating the app and its effect on quality of life will address the shortage of literature-backed mHealth interventions, and attempt to validate new approaches to benefitting AYA oncology patients in the digital world.

Conflicts of Interest

None declared.

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Abbreviations

ANOVA: analysis of variance
AYA: adolescent and young adult
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of life Questionnaire Core 30
HRQoL: Health Related Quality of Life
MAST: Model for Assessment of Telemedicine Applications
mHealth: mobile health
PPI: patient and public involvement
QoL: quality of life

Protocol

Implementation and Evaluation of a Smartphone-Based Telemonitoring Program for Patients With Heart Failure: Mixed-Methods Study Protocol

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Abstract

Background: Meta-analyses of telemonitoring for patients with heart failure conclude that it can lower the utilization of health services and improve health outcomes compared with the standard of care. A smartphone-based telemonitoring program is being implemented as part of the standard of care at a specialty care clinic for patients with heart failure in Toronto, Canada.

Objective: The objectives of this study are to (1) evaluate the impact of the telemonitoring program on health service utilization, patient health outcomes, and their ability to self-care; (2) identify the contextual barriers and facilitators of implementation at the physician, clinic, and institutional level; (3) describe patient usage patterns to determine adherence and other behaviors in the telemonitoring program; and (4) evaluate the costs associated with implementation of the telemonitoring program from the perspective of the health care system (ie, public payer), hospital, and patient.

Methods: The evaluation will use a mixed-methods approach. The quantitative component will include a pragmatic pre- and posttest study design for the impact and cost analyses, which will make use of clinical data and questionnaires administered to at least 108 patients at baseline and 6 months. Furthermore, outcome data will be collected at 1, 12, and 24 months to explore the longitudinal impact of the program. In addition, quantitative data related to implementation outcomes and patient usage patterns of the telemonitoring system will be reported. The qualitative component involves an embedded single case study design to identify the contextual factors that influenced the implementation. The implementation evaluation will be completed using semistructured interviews with clinicians, and other program staff at baseline, 4 months, and 12 months after the program start date. Interviews conducted with patients will be triangulated with usage data to explain usage patterns and adherence to the system.

Results: The telemonitoring program was launched in August 2016 and patient enrollment is ongoing.

Conclusions: The methods described provide an example for conducting comprehensive evaluations of telemonitoring programs. The combination of impact, implementation, and cost evaluations will inform the quality improvement of the existing program and will yield insights into the sustainability of smartphone-based telemonitoring programs for patients with heart failure within a specialty care setting.

KEYWORDS

heart failure; telemedicine; self-management; health services research; costs and cost analysis

Introduction

Background

Currently, one of the greatest challenges for health care systems worldwide is the growing fiscal and social burden of preventing and managing chronic diseases [1]. Heart failure (HF) is one of the most expensive chronic diseases, partly because 50% of patients with HF get readmitted within 1 year [2]. Evidence suggests approximately half of all readmissions are preventable and result from inadequate discharge teaching, nonadherence to medication, or failure to have early follow-up with a clinician [3].

There is mounting evidence that embedding self-care within existing health care services provides an effective model to meet these needs for a number of chronic diseases, including HF [4-7]. Although more traditional self-care interventions such as health coaching or patient education can be effective [8,9], their implementation often proves challenging [10,11]. Health information technology is one avenue that can support the delivery of self-care interventions. For example, telemonitoring (TM) is thought to be crucial to offer patients the right care at the right time [12] by allowing patients to collect clinical data at home, which is then transmitted via technology to be viewed and acted upon by a clinician at a distant location [13].

In HF, meta-analyses conclude that TM lowers the utilization of health services, improves HF health outcomes, and improves health-related quality of life (QoL) [14-20]. However, results vary widely between individual trials [21], and 2 of the largest studies, the Tele-HF [22] and BEAT-HF trials [23], reported null results. One problem is that results come from trials of varying quality, and there is often little discussion about the intervention itself or the degree to which the patients have adhered to it over the course of the study [24]. Furthermore, studies looking at the implementation of TM have identified technical, cost, organizational, and behavioral barriers, which may explain why these technologies are not yielding consistent positive outcomes [12,25]. In addition, this may explain why, despite some evidence of cost-effectiveness [26], there is still inconclusive evidence regarding the impact of TM in terms of its cost to patients with HF [26].

Although the ubiquity of mobile phones is believed to have the potential to make TM interventions more accessible and cost-effective [27,28], additional knowledge gaps exist in the emerging use of smartphones for TM of chronic diseases. Randomized controlled trials (RCTs) employing mobile phone–based TM interventions have been conducted and have shown similar positive results to those reported for more traditional TM [29,30]. However, this type of TM is novel, and therefore, there have been no comprehensive implementation studies on smartphone-based TM interventions completed to date.

Implementation of a Smartphone-Based Telemonitoring Program

The Intervention

An algorithm-based smartphone-based TM program for patients with HF, called the Medly Program, is being implemented as part of the standard of care at the University Health Network's Ted Rogers Center of Excellence for Heart Function in Toronto, Canada (hereafter referred to as the HF clinic). The objective of the Medly Program is similar to other HF TM programs: improve patient self-management and decrease health care utilization [31]. Patients enrolled in the Medly Program will receive a Medly kit that includes a smartphone (Samsung Galaxy Grand Prime) with a limited data plan and the Medly app already downloaded. In addition, patients receive a Bluetooth-enabled weight scale and blood pressure cuff. Patients are instructed to take daily weight and blood pressure readings using these devices and record their symptoms using the Medly app first thing in the morning. Automated self-care instructions are immediately displayed in the Medly app after these 3 parameters are processed by an algorithm that was developed in close consultation with HF clinicians. In addition, patients have access to graphs displaying historical trends for these parameters. To assist in compliance, patients receive an automated call on their primary phone line if they have not taken their readings before 10 AM. The Medly Program is initially providing patients with all the equipment to mitigate the potential operational and software development challenges of offering the service on different devices during the critical early stages of implementation. However, a transition to a *bring your own device* model is planned, which would enable patients with smartphones to use their own devices by downloading the Medly app.

If there are signs of deteriorating health of a patient, the Medly algorithm generates an alert to a HF clinician who is part of the patient's care team. The alerts are made available to clinicians in 2 formats. The first is through an automated email containing the latest weight, blood pressure, and symptoms along with the patient's target ranges. In addition, the email contains the patients' latest medication list and HF–related laboratory results, and contact information. Second, clinicians can choose to view the alerts by accessing a secure Web portal that presents a list of all the alerts triggered. Here, clinicians can review details of the latest alert and graphs showing historical weight, blood pressure, symptoms, and HF–specific laboratory results, which are visually contextualized according to the patient's target ranges. The clinician will follow-up with the patient depending on the clinical need, documenting all actions and decisions taken

in response to the alert in the hospital electronic medical record (EMR).

The Medly Program is intended to be delivered as part of the standard of care; as such, the goal is for it to be seamlessly integrated within the existing workflows of the HF clinic. Before deployment, a service blueprint was created through ethnographic methods including observation and informal interviews with clinicians and support staff in the HF clinic. This helped identify areas where the processes of the Medly Program could be incorporated. In addition, an RCT of 100 patients with an embedded qualitative component was previously conducted in the HF clinic with an earlier version of the Medly system. This study concluded that patients receiving the intervention experienced improvements in QoL and self-care maintenance compared with a control group [30]. Lessons learned from this RCT helped justify the decision to implement the Medly Program as part of the standard of care and informed the program's implementation strategy. The current program offers an opportunity to evaluate the implementation and effectiveness of Medly under real-world conditions.

User Training and Support

Training as to how to use the Medly app and associated devices is provided to patients at the time of enrollment into the Medly Program by a telehealth analyst. Clinicians monitoring patients through the Medly system participated in a formal training session approximately 1 month before program deployment. Both patients and clinicians are provided with a user manual to supplement the in-person training along with contact information of the telehealth analyst who offers technical support during normal business hours.

Evaluation Objectives and Research Questions

Objective 1

The first objective is to evaluate the impact of the Medly Program on health service utilization, patient health outcomes, and their ability to self-care. Alerts sent to patients and clinicians will help identify periods of symptom exacerbation and volume overload. The impact of this is expected to permit earlier intervention for worsening conditions, thus avoiding trips to the emergency department (ED) and hospitalizations. For patients who are enrolled into the Medly Program on hospital discharge, the program is expected to reduce 30-day readmission rates. In addition, participation in the Medly Program is expected to improve patients' ability to self-care, leading to improved clinical outcomes and QoL.

Objective 2

The second objective is to evaluate the degree to which the Medly Program was implemented as intended and to identify the contextual barriers and facilitators of implementation. This objective will answer the following questions:

- To what extent did the HF clinic implement the Medly Program as intended?
- What contextual factors influence the implementation of the Medly Program?
- What adaptations were needed to implement and sustain the program within existing clinical workflows?

Objective 3

The third objective is to describe patient usage patterns to determine adherence and other behaviors in the Medly Program. This objective will answer the following questions:

- To what degree do patients adhere to the Medly Program and how do adherence patterns change over time?
- What factors influence patient adherence?

Objective 4

The fourth objective is to evaluate the costs associated with the implementation of the TM program from the perspective of the health care system (ie, public payer), the hospital, and patients.

Methods

Overview of the Study Design and Evaluation Framework

Data for the 4 objectives will be collected using mixed-methods. This approach will include a multiple pre-and posttest design for the evaluation of patient-level impacts, patient adherence, and cost. Quantitative data will include data collected as part of the standard of care (including health care utilization data and laboratory results obtained using a chart review) and usage data from the TM system. Additional patient-level data will be collected using questionnaires at baseline, 1 month, 6 months, 12 months, and 24 months. The qualitative component will take the form of an embedded single case study [32]. The 2 embedded subunits of analysis include clinicians and patients, as it relates to their adoption and use of the Medly system. The case is defined as the Medly Program at the HF clinic for the duration of 1 year starting from the program's launch date (August 23, 2016). Qualitative methods, including semistructured interviews and document reviews, will be used to gain insights regarding patient self-care practices (objective 1), the barriers and facilitators to program implementation (objective 2), and explanations for patient adherence and usage of the system (objective 3).

Study Participants

Representatives from all stakeholder groups involved in the implementation of the Medly Program will be recruited for participation.

Patients

Patients can be enrolled into the Medly Program provided they (1) are 18 years or older, (2) have been diagnosed with HF and are followed by a cardiologist at the HF clinic, (3) can speak and read English (or have an informal caregiver who does) to adequately understand the text prompts in the Medly app, and (4) are able to comply with using Medly (eg, able to stand on the weight scale, able to answer symptom questions). As the Medly program is being implemented as part of the standard of care, there is no explicit exclusion criteria for participating in the program and its evaluation. The duration of program participation will be decided by patients and their treating cardiologist on an individual basis.

Upon enrollment into the Medly Program, patients will be presented with the option of answering questionnaires and

participating in interviews related to the program evaluation. Patients will be asked to sign a written consent form before participating in the evaluation.

Program Staff

All members of the Medly Program staff will be asked to participate in semistructured interviews. These include clinicians providing care for patients with HF in the HF clinic (n=7), telehealth analyst (n=1), project manager (n=1), and members of the implementation team (n=2). These individuals will be asked to sign a consent form before their first interview.

Data Collection and Analysis

Objective 1: Measuring the Impact of the Medly Program

Impact Indicators

The primary outcome for evaluating the impact of the Medly Program is the number of hospitalizations because of HF in the 6 months before versus the 6 months after enrollment. Secondary impact outcomes comparing 6-month to baseline values are described below.

Health Service Utilization

The number of hospitalizations (all-cause), 30-day readmission rate, days in hospital (HF and all-cause), number of ED visits (HF and all-cause), visits to family doctor (HF and all-cause), number of HF–related outpatient visits, and changes to medication will be recorded.

Left Ventricular Fraction and Laboratory Tests

The following HF–specific clinical parameters will be collected: left ventricular ejection fraction (LVEF), brain natriuretic peptide (BNP), creatinine, sodium, potassium, hemoglobin, and uric acid levels.

Mortality and Prediction of Survival

Patient mortality will be tracked. In addition, the Seattle Heart Failure Model (SHFM) will be calculated at program entry. Projected SHFM survival versus actual survival will be compared [33]. The calculation of this score requires data on age, gender, New York Heart Association classification, weight, LVEF, systolic blood pressure, list of medications (including diuretics), laboratory results (hemoglobin, lymphocytes, uric acid, total cholesterol, and sodium), and QRS interval.

Dyspnea

Patients will be asked to describe their level of breathlessness using a visual analogue scale for dyspnea on a scale ranging from 0 (no shortness of breath) to 10 (shortness of breath is the worst it can be).

Quality of Life

The EQ-5D-5L is a measure of generic health status and will be administered to all patients as a measure of QoL [34,35]. This 5-item instrument has undergone validity and reliability testing for several conditions including HF. Due to the generic nature of this measure, it is recommended that it be administered

along with supplementary measurements to capture more disease-specific aspects related to QoL. Hence, the Minnesota Living with Heart Failure Questionnaire (MLHFQ) will also be administered. The questionnaire contains 21 items scored on a 5-point Likert scale, the responses of which are summed to produce a total score and subscores for the domains of physical and emotional QoL. The MLHFQ is widely used in studies involving HF–related QoL and has been shown to have a high level of reliability and validity [36].

Self-Care

The self-care of HF index asks respondents to respond to 22 items on a 4-point Likert scale to assess their ability to self-care across 3 subscales (maintenance, management, and confidence). The tool has undergone validity and reliability testing involving patients with HF [37].

Demographic Variables

Demographic information will also be collected using a questionnaire, which includes questions on the following: age, sex, income, native language, living arrangements (living alone, with a partner, or other), whether or not they have a caregiver (formal or informal), and type of living areas (eg, urban, suburban, or rural). In addition, patient comorbidities will be tracked. Finally, questions will be asked to assess the patient's experience and comfort level with technology and smartphones, including frequency of use.

Data Acquisition

Data collection will occur at baseline, 1 month, 6 months, 12 months, and 24 months, or until the patient exits the program. Data collected in addition to the primary evaluation period (baseline to 6 months) will provide an opportunity for post-hoc analyses aimed at quality improvement, including recommended duration of use. For example, the 1-month time point was included to determine if the bulk of changes to self-care and QoL occur immediately after enrollment. Similarly, longitudinal data will help determine whether patient-level impacts are sustained or change when using the system long term.

Health service utilization, laboratory results, mortality, prediction of survival, and select demographic information will be obtained from the hospital EMR. In addition, health service utilization information will be verified by patient participants through self-reports via a questionnaire.

Baseline and follow-up questionnaires containing the validated survey tools listed in Table 1 will be distributed to patients during regularly scheduled visits. Upon study enrollment, patients will be asked whether they prefer to be mailed the questionnaire or completing it using an online survey tool (SurveyMonkey [38]) in the event that they do not have a clinic visit scheduled for the data collection time point. In these situations, the questionnaires will be sent to the patient according to the preferred format and they will be given 2 weeks to respond, after which a member of the evaluation team will call the patient to remind them to complete the questionnaire.

Table 1. Timing of outcome assessments for the impact evaluation.

Domain and measure	Baseline	1 month	6 months	12 months	24 months	Exit
Health service utilization						
30-day readmission		X[a]				
Number of hospitalizations	X		X	X	X	X
Number of days in hospital	X		X	X	X	X
Number of emergency department visits	X		X	X	X	X
Number of heart failure-related outpatient visits	X		X	X	X	X
Number of visits to family doctors	X		X	X	X	X
Changes to medication	X		X	X	X	X
Clinical outcomes						
Left ventricular ejection fraction	X			X	X	
Blood work: BNP[b], creatinine, sodium, potassium, hemoglobin, and uric acid	X		X	X	X	X
Visual analogue scale for dyspnea	X	X	X	X	X	X
SHFM[c]	X					
Self-care						
SCHFI[d] [37]	X	X	X	X	X	X
EQ-5D-5L[e] [34,35]	X	X	X	X	X	X
MLHFQ[f] [36]	X	X	X	X	X	X

[a]X: data is collected at this time point.

[b]BNP: brain natriuretic peptide.

[c]SHFM: Seattle Heart Failure Model.

[d]SCHFI: Self-Care of Heart Failure Index.

[e]EQ-5D-5L: EuroQol five-dimensional.

[f]MLHFQ: Minnesota Living with Heart Failure Questionnaire.

Planned Analyses

The primary analyses will be paired Student t tests and Wilcoxon signed rank tests comparing baseline and 6-month values for all patient-level outcomes. For patients enrolled in the Medly Program on hospital discharge, the 30-day readmission rate will be compared with the readmission rate before the launch of the Medly Program, as determined using hospital administrative data. Secondary analyses aimed at determining the longitudinal impact of the Medly Program (ie, using outcome data from the additional time points), and the correlation of independent variables (eg, patient characteristics and adherence rates) with outcomes will be analyzed using general linear mixed model procedures. In addition, descriptive statistics will be produced for all variables collected, which may inform necessary subgroup analyses. All statistical analyses will be performed using the statistical software application SPSS (IBM Corporation, USA) [39].

Power Consideration

We will aim to recruit at least 108 patients into the Medly Program at the HF clinic before analyses of patient-level outcomes are undertaken. This number is based on being able to detect a small effect size (Cohen d=0.3) in the number of hospitalizations because of HF within the first 6 months of enrollment with 80% power and an alpha of .05 (two-sided) [40]. This number considers that approximately 20% of patients will be "lost to follow-up," which includes patient mortality and those who withdraw from the program before the 6-month time point. We anticipate recruiting this number in the first 18 months of the program.

Objective 2: Implementation Evaluation

The mixed-methods implementation evaluation will be guided by the framework by Proctor et al, which describes outcomes that can serve as indicators of implementation success [41], and the Consolidated Framework for Implementation Research (CFIR). The CFIR describes factors influencing implementation success according to 5 domains: (1) intervention characteristics, (2) outer setting, (3) inner setting, (4) characteristics of individuals, and (5) process [42].

Table 2. Implementation outcome indicators.

Implementation outcome	Definitions[a]	Indicator
Adoption	The intention, initial decision, or action to try or employ an innovation or evidence-based practice. Adoption may also be referred to as "uptake"	Number of clinicians having decided to use Medly to monitor patients
Implementation cost	The cost impact of the implementation effort	See objective 4 for cost outcomes associated with implementation of the Medly Program
Feasibility	The extent to which a new treatment, or an innovation, can be successfully used or carried out within a given agency or setting	Number of patients enrolled; rate of patient enrollment; number of patient-initiated dropouts from the program; number of physician-initiated dropouts from the program—or no uptake
Fidelity	The degree to which an intervention was implemented as it was prescribed in the original protocol or as it was intended by the program developers	Number and nature of calls or emails made to the telehealth analyst; proportion of the number of—alerts acknowledged over the total number of alerts, phone calls to patients over the total number of alerts triggered, and false or inappropriate alerts over the total alerts triggered
Penetration	The integration of a practice within a service setting and its subsystems	Percentage of clinicians using Medly over the total number of potential clinician users in the HF clinic

[a]Definitions are based on the definitions provided by Proctor et al [41].

Implementation Outcome Indicators

Implementation outcomes are defined by Proctor et al as "the effects of deliberate and purposive actions to implement new treatments, practice, and services" [41]. A total of 5 implementation outcomes were selected as quantitative indicators and are presented in Table 2. These data will be obtained from the hospital's EMR, the Medly system's audit trails, and technical support logs.

Semistructured Interviews With Program Staff

Separate semistructured interview guides based on the constructs in the CFIR will be formulated for each category of program staff previously outlined. Interviews will be conducted at baseline, 4 months, and 12 months to align with the different phases of Stetler et al's typology of formative evaluations [43]. The interviews are expected to last approximately 30 min and will be conducted at a location convenient to the participants. All interviews will be audiotaped for later transcription and analysis.

Planned Analyses

Descriptive statistics will be produced for the indicators of the implementation outcome to provide an objective measure of implementation success.

Furthermore, 2 independent researchers will analyze interview transcripts and documents using the Framework Method of qualitative analysis [44]. An initial round of coding will use a deductive approach by looking for themes that match the constructs in the CFIR. A second round of coding will be inductive using an open coding approach, which will involve researchers looking for unexpected themes that are not represented in the guiding CFIR framework. Throughout the analysis, both reviewers will discuss the themes and codes from their independent analyses to come up with a single analytical framework. This finalized framework will be applied in a final coding of all transcriptions using NVivo (QSR International, Doncaster, Victoria, Australia) [45].

Quantitative and qualitative data will be triangulated such that the interview data will help explain success or failure of the implementation.

Objective 3: Describing Patient Adherence and Usage Patterns

A sequential explanatory mixed-methods approach [46] will be used consisting of a quantitative measurement of patient adherence and semistructured interviews with patients at 4 time points.

Patient Adherence

Adherence will be assessed by analyzing patient usage rates of the Medly system—specifically, the proportion of days for which the patient took a complete reading (weight, blood pressure, and symptoms) over the previous 30 days. Usage data will be obtained and exported on a regular basis through Google Analytics [47].

Semistructured Interviews

A sample of patients enrolled in the Medly Program will participate in semistructured interviews aimed at understanding reasons for adherence or nonadherence and their general experiences with the Medly Program. Interview guides will be formulated based on the constructs of the Unified Theory of Acceptance and Use of Technology 2 [48]. For example, we will explore how patients' expectations, ease of use of the intervention, facilitating conditions (eg, quality of technical support services), and the direct or indirect influence of clinicians and loved ones could explain levels of uptake, adherence, and use. Unlike adherence, which will be calculated for all patients enrolled in the Medly Program, interviews will be conducted until information saturation is reached using maximum variation sampling [49] based on age, sex, experience with technology, health status, time since enrollment, and level of adherence. As recommended by Francis et al for theory-based interview studies, an a priori target of 10 patients is being set as the initial analysis sample [50]; however, interviews will continue until no new themes emerge [50]. For patients who

withdraw from the Medly Program before the end of the evaluation period, reasons for this withdrawal will be documented as part of standardized off-boarding procedures and a sample will be asked to participate in an interview. The interviews are expected to last 20 to 30 min and will be conducted in a quiet and private space within the clinic (eg, consultation room) during a regular clinic visit or over the telephone. All interviews will be audiotaped and transcribed for later analysis.

Planned Analyses

Monthly adherence rates will be examined using descriptive statistics to identify any patterns in the increase or decrease of patient adherence to Medly over time. In addition, general linear mixed model procedures will be performed to determine if any baseline patient characteristics (eg, age, sex, and HF severity) or time since program enrollment predicts patient adherence to the Medly system. Semistructured interviews will be analyzed using the Framework Method [44], as previously described.

Objective 4: Cost Impact of Implementing the Medly Program

The costs associated with implementing the Medly Program will be determined from the perspectives of the public payer, hospital, and patient. In reporting these results, costs will be interpreted in relation to the patient-level impacts determined in objective 1.

Data Acquisition

Costs will be calculated using a 6-month time frame. Specifically, we will compare costs before the implementation of the Medly Program (assessed at baseline) versus the costs after enrollment of patients into the program (measured at 6 months). This time frame was chosen because it represents the time horizon over which most of the health effects and costs of using the Medly Program are expected. Most of the cost variables will be self-reported by patients and triangulated using administrative data whenever possible (eg, EMR data). Therefore, questions related to the cost will be added to the patient outcome questionnaires (objective 1) and will be administered at baseline and 6 months.

Public Payer Perspective

Costs to the public payer will be determined by looking at health care utilization of patients enrolled in the Medly Program before versus after their enrollment. These will include hospitalizations, ED visits, HF clinic visits, family physician visits, and use of home care services. In addition, costs for inpatient medications will be considered.

Hospital Perspective

Costs from the hospital perspective will be valued based on time spent by human resources involved in the Medly Program. This time will be converted to costs based on those individuals' respective salaries. This will include time the clinicians spent reviewing and responding to Medly alerts as well as time the clinicians spend in training sessions, learning to use the system, and seeking technical support. In addition, costs for the hospital perspective will include equipment costs (Medly kit, smartphone data plan, and server) and the salary for employing a telehealth analyst responsible for recruiting, training, onboarding, managing inventory support, and providing training.

Patient Perspective

Costs for patients will primarily be determined by the time they spend accessing care for HF. This will involve determining their employment status and annual income as well as time they spend traveling to and from appointments, time spent at appointments, and how much work time was missed because of their HF condition (vacation or unpaid). In addition, this will include the time patients spent learning to use the Medly system, time spent using the system, and time getting technical support. Additional costs considered include travel, parking, and all other out-of-pocket costs related to accessing care or using the intervention. Moreover, time of informal caregivers (eg, friend or family member who helps the patient to manage their HF) will be valued as part of the patient perspective. Costs for informal caregivers will be based on the average hourly rate of personal support workers.

Results

The Medly Program was launched in August 2016. As of April 4, 2018, 166 patients have been enrolled. The primary impact analysis is expected to be conducted by January 2019.

Discussion

This study aims to evaluate the implementation and impact of a smartphone-based TM program being implemented as part of the standard of care in a specialty care setting in a large Canadian city.

Limitations

Unlike TM systems evaluated in the context of academic research, the lack of strict patient inclusion and exclusion criteria for the Medly Program has the potential to lead to heterogeneity among evaluation participants, which will make it difficult to generalize the results to other health care settings. Another important limitation is that the nature of this evaluation and the availability of data do not allow for a distinct comparator group. Without discounting these limitations, we believe that one of the strengths of this evaluation is its pragmatic nature and that these threats to internal and external validity will be mitigated through a detailed description of the context and participants when results are reported. The interpretation of the Medly Program evaluation results will include comparisons with previous TM RCTs conducted within the HF clinic [30] and other comparable settings, as well as other RCTs evaluating interventions designed to promote self-care through education and health coaching conducted within the HF clinic [51]. This is possible because of the selection of outcome metrics common in other TM studies.

Conclusions

Unlike other TM studies that focus primarily on quantitative outcomes, this evaluation will also examine the context and mechanisms that lead to them. Therefore, this pragmatic mixed-methods study will allow for an interpretation of results using realist evaluation principles [52]. The information gathered

during this evaluation will inform if, and how, a smartphone-based TM system improves the self-care capacities, clinical management, and health outcomes of patients with HF. This evaluation will lead to quality improvement of the current program and provide evidence that will inform the implementation and sustainability of other TM programs.

Authors' Contributions

PW and ES led the overall design of the evaluation; HJR, AL, and JAC also contributed to the design. PW drafted the manuscript, and ES, HJR, AL, and JAC edited and reviewed the manuscript. ES is the principal investigator of this evaluation.

Conflicts of Interest

None declared.

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Abbreviations

BNP: brain natriuretic peptide
CFIR: Consolidated Framework for Implementation Research
ED: emergency department
EMR: electronic medical record
EQ-5D-5L: EuroQol five-dimensional
HF: heart failure
LVEF: left ventricular ejection fraction
MLHFQ: Minnesota Living with Heart Failure Questionnaire
QoL: quality of life
RCTs: randomized controlled trials
SCHFI: Self-Care of Heart Failure Index

SHFM: Seattle Heart Failure Model
TM: telemonitoring

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Protocol

Conceptualization and Implementation of the Central Information Portal on Rare Diseases: Protocol for a Qualitative Study

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This is a corrected version. See correction statement: http://www.researchprotocols.org/2018/9/e11248/

Abstract

Background: Recently, public and political interest has focused on people living with rare diseases and their health concerns. Due to the large number of different types of rare diseases and the sizable number of patients, taking action to improve the life of those affected is gaining importance. In 2013, the federal government of Germany adopted a national action plan for rare diseases, including the call to establish a central information portal on rare diseases (Zentrales Informationsportal über seltene Erkrankungen, ZIPSE).

Objective: The objective of this study, therefore, was to conduct scientific research on how such a portal must be designed to meet the needs of patients, their families, and medical professionals, and to provide high-quality information for information seekers.

Methods: We chose a 3-step procedure to develop a needs-based prototype of a central information portal. In the first step, we determined the information needs of patients with rare diseases, their relatives, and health care professionals by means of qualitative interviews and their content-analytical evaluation. On the basis of this, we developed the basic structure of the portal. In the second step, we identified quality criteria for websites on rare diseases to ensure that the information linked with ZIPSE meets the quality demands. Therefore, we gathered existing criteria catalogs and discussed them in an expert workshop. In the third step, we implemented and tested the developed prototypical information portal.

Results: A portal page was configured and made accessible on the Web. The structure of ZIPSE was based on the findings from 108 qualitative interviews with patients, their relatives, and health care professionals, through which numerous information needs were identified. We placed particularly important areas of information, such as symptoms, therapy, research, and advisory services, on the start page. Moreover, we defined 13 quality criteria, referring to factors such as author information, creation date, and privacy, enabling links with high-quality information. Moreover, 19 users tested all the developed routines based on usability and comprehensibility. Subsequently, we improved the visual presentation of search results and other important search functions.

Conclusions: The implemented information portal, ZIPSE, provides high-quality information on rare diseases from a central point of access. By integrating the targeted groups as well as different experts on medical information during the construction, the website can assure an improved search for information for users. ZIPSE can also serve as a model for other Web-based information systems in the field of rare diseases.

Registered Report Identifier: RR1-10.2196/7425

Introduction

Finding Reliable Information on Rare Diseases as a Major Challenge

In Germany, an estimated 4 million people live with rare diseases [1]. Rare diseases, as defined by the Community Action Programme on Rare Diseases 1999-2003, are those with a prevalence of ≤1 per 2000 persons in the European Union [2]. Accordingly, of all known diseases, about 7000 can be considered rare. Even though causes and symptoms can widely vary, patients with rare diseases and their families often face similar challenges [3]. Among others, the affected people often lack reliable information about their own or their relatives' disease due to unfamiliarity with information services or information retrieval systems. Additionally, for physicians who rarely encounter rare diseases in their daily practice, finding reliable information on diagnosis and treatment is a major challenge. Consequently, patients often wander from one doctor to another for years, until they receive a correct diagnosis and obtain access to specialized care. Therefore, in 2013, the federal government adopted a "National Action Plan on Rare Diseases" to improve patients' health situation. Establishing an information system suitable for patients is one component of a broader set of measures to achieve this goal [4].

Currently, patients, their families, and health professionals have some difficulties in finding high-quality information on rare diseases [3]. Although there are plenty of websites, portals, and databases on rare diseases in the World Wide Web, including those on specific conditions and rare diseases in general, people do not know about these websites or struggle to find them in the vastness of the internet. Moreover, not every information website is suitable for different types of users and their specific needs. One of the largest databases on rare diseases in Europe, for instance, is Orphanet [5], which provides comprehensive information on a large number of rare diseases. Nonetheless, the information offered on this database meets the requirements of health professionals more than those of laypersons. Furthermore, there are some national and international information services, such as the National Organization for Rare Diseases in the United States and the Alliance of Chronic Rare

Diseases in Germany [6,7]. However, the former as well as other foreign language offerings are not suitable for all people in Germany affected by or interested in knowing about the disease, due to language barriers. Yet, it is essential to understand disease information accurately. The latter only contains information on a small number of rare diseases, such that its usability is limited.

Apart from the aforementioned sources, centers for rare diseases and patient organizations often provide comprehensive and reliable information. Especially for patients and their relatives, the latter are important contact partners that help them access specialized care or offer advice on all questions relating to their disease. For people affected by a rare disease, physicians can be another important source of information [8-12]. However, apart from those who deal with these conditions on a regular basis, for instance, physicians working in centers for rare diseases, general practitioners, as well as specialists in private practice often lack such information.

Developing a Central Information Portal on Rare Diseases

Therefore, this project aimed to conceptualize and implement a central information portal on rare diseases (ZIPSE) on the internet, through which people affected by a rare disease, their families, and relatives, as well as medical professionals can obtain access to high-quality information in German language. This should be done based on scientific methods and with the involvement of the different target groups. However, the portal's editorial staff will not be generating the information provided on ZIPSE. Rather, it will identify, check, and link with ZIPSE, existing information sites on rare diseases, if they provide user-relevant information.

Methods

Evaluating the Information Needs of Patients, Relatives, and Health Care Professionals

To develop an information portal that suits the needs of patients, their relatives, and health professionals equally, over the entire course of the project, we aimed to integrate all target groups who may use the portal in the future. To ensure that the

information provided on ZIPSE fulfills the needs of each target group as closely as possible, we initially evaluated the information needs of patients, relatives, and people working in the health care sector. Due to insufficient data on information needs in the field of rare diseases, we decided to use qualitative methods. For patients and their families, we developed an interview guide for eliciting information about their medical history, diagnostic processes, experience of living with the disease, and information searches. As many patients and their relatives ultimately join patient organizations, which can influence their awareness and knowledge of rare diseases, we asked them about their early experience of information gathering. To test whether the interview guide is suitable to identify individuals' information needs, it was pretested with 2 patients and 1 relative. We subsequently adjusted the guide for those diagnosed before or shortly after birth, who could not remember their diagnostic paths.

To recruit a broad and balanced sample, we formed 11 groups of rare diseases at the beginning of this study, which represented a comprehensive variety of rare diseases. We planned to interview 6 patients or their family members in each group. Moreover, we conducted 10 interviews with patients who had waited for at least 10 years for diagnosis. Thus, we intended the sample to comprise 76 patients and close relatives. However, upon saturation of interview data, we found that a smaller sample was sufficient. Participants were recruited through the Freiburg Center for Rare Diseases at the University Medical Center Freiburg, University of Freiburg, Germany.

Our final sample involved a total of 68 participants, including 55 patients and 13 relatives (Table 1). Due to limited access to some patient groups, we could not ascertain the targeted number of interviews in all groups of diseases. However, as it became clear during the study that further interviews do not lead to further identification of information needs, no further recruitment was done.

To identify the information needs of health care professionals, we decided to conduct expert interviews. For this, we developed and pretested different structured interview guides for the different groups surveyed. In our sample, we considered physicians who are not related to centers of rare diseases and hence are inexperienced in information searches on rare diseases. These included general practitioners and medical specialists in private practice, as well as clinicians. Moreover, we interviewed medical technical assistants from in and out-patient care. Thus, experts in the care system, who are specialists in the field of rare diseases and guide patients or people suspected of suffering from a rare disease by the appropriate points of contact, comprised the interview sample. Apart from sociodemographic variables such as gender and age, other parameters integrated in sample selection included the nature of practice and geographical location. We did not strive for a certain sample size at the beginning of this study, but rather tried to reach theoretical saturation by conducting as many interviews as necessary with each sample group (physicians, medical technical assistants, and experts in rare diseases). The results of the

interviews with the doctors were validated in a quantitative Delphi survey. Our final sample of health care professionals involved 28 physicians, 6 nurses, 4 guides, and 2 biologists.

We analyzed the interviews according to the structured content analysis method developed by Philipp Mayring [13]. Each audio recording was verbally transcribed and transferred to the MAXQDA (Verbi Software GmbH, Berlin) analysis software. Subsequently, 4 researchers examined the interviews independently, to mark all text passages providing information on people's information needs.

Afterwards, an extensive system of categories using a deductive-inductive approach was developed. Therefore, the researchers processed 5 interviews to transfer the contents from the marked text passages into main- and sub-categories that represent detailed aspects of people's information needs (inductive approach). Additionally, the researchers derived several categories (deductive approach) based on previous research on current information on rare diseases from the internet and published literature review [14-17]. These were integrated into the inductive categories stemming from the text (inductive approach). Then, we applied the system of categories to the rest of the marked text passages and modified or rather complemented it, if necessary.

Furthermore, we presented and discussed the information needs found in the interviews in 4 focus groups, to enable consensual validation. Participants of the focus groups were recruited chiefly from the initial study sample. In addition, some consultants from patient organizations were invited to participate. On the basis these results, the basic structure of the ZIPSE portal and information paths were developed.

Defining the Quality Criteria for Websites on Rare Diseases

Defining the quality criteria for websites on rare diseases was the next step, as, owing to the large number of rare diseases, we planned to provide references to other internet sites instead of providing primary information. Therefore, we examined all quality certifications, catalogs of criteria, and recommendations for information on the Web existing in Germany, and compiled them in 1 conceptual map. In a workshop, several experts on quality of online information discussed this conceptual map with the project team to decide which quality criteria should be considered while linking information websites with the ZIPSE portal. Accordingly, we created a set of specific quality criteria on rare diseases.

Additionally, we conducted extensive research on existing German information websites on rare diseases to create a basic database for the subsequent inclusion of websites in accordance with the quality criteria. Therefore, we screened the internet for information websites on rare diseases using the German Orphanet list of rare diseases and their synonyms [18]. This list included all registered rare diseases. Several research assistants searched the most common browsers for all these diseases, and subsequently screened the first 20 entries offering information on the specific disease on which they sought information.

Table 1. Patient and relative demographics.

Characteristics in participants (N=68)	Statistics
Age (years), mean	50.5
Gender, n (%)	
Female	45 (66)
Male	23 (34)
Rare disease, n (%)	
Genetic skin diseases	10 (15)
Skeletal dysplasia	7 (10)
Neuromuscular diseases	9 (13)
Genetic eye diseases	4 (6)
Connective tissue diseases	5 (8)
Genetic kidney diseases	6 (9)
Cystic fibrosis and pulmonary diseases	7 (10)
Congenital blood formation disorders	4 (6)
Immunodeficiency	7 (10)
Congenital metabolic disorder	7 (10)
Genetic diseases of the digestive tract	2 (3)
Status, n (%)	
Patients	55 (81)
Relatives	13 (19)

Technical Implementation and Usability Tests

We used the information paths and functions developed based on the derived information needs to develop a prototype information portal. Thus, we set up a Uniform Resource Locator, on which essential elements could be activated and tested it concomitantly [19]. Initially, within the framework of the focus groups described above, we introduced patients and relatives, who had already participated in the interviews, to the preliminary version of the information portal, and they provided their opinion. Thus, we derived potential for improving the design of the home page of the website and of the search function within the portal. Subsequently, to check whether the derived information paths corresponded to people's information needs, we conducted usability tests with patients, their relatives, and physicians. For this purpose, we asked the testers to browse through the portal and search for specific information on their disease while thinking aloud. Among the testers were 9 patients with rare diseases and 10 physicians, who did not participate in the interviews. As a result, authors could identify at which points of their search users may have problems in acquiring the information sought. Moreover, we measured their satisfaction with the use of the portal in personal discussions with the testers. A written survey was not conducted due to the small number of tests.

Results

Information Needs of Patients, Relatives, and Health Care Professionals

The findings of this study revealed a variety of information needs of patients with rare diseases and their families, which are published in detail elsewhere [20]. On the basis of content analysis, we derived various information areas relevant for the interviewees. First, we found that people's information needs varied depending on the type and stage of illness. Shortly after diagnosis, the affected individuals reported the need for easily comprehensible and concise information, enabling an overall understanding of the disease, its causes, symptoms, and impact on their everyday life. Moreover, the participants stated that they wished for information on personal contacts of other patients or their relatives after they had received a diagnosis. At a later stage, people often mentioned the need for more detailed information on their disease. For example, they would like to know if there were any research efforts in which they or their relatives could participate. Knowledge about research on their illness is an important factor for many patients because it helps them cope with the illness and remain confident. Especially for those suffering from a severe rare disease that has not yet been researched intensively, this can be of enormous importance.

Content analysis showed that health care professionals' needs partly overlapped with those of patients and their relatives. According to the respondents, doctors preferred to have basic information (eg, regarding prevalence or the course of the

disease) about rare diseases before diagnosing the disease and assistance in the diagnostic process (eg, by obtaining information on special laboratories or specialized centers). Once the disease is diagnosed, the information needs to be shifted to the field of therapy coordination. The respondents assigned great importance to information about the counseling and care of patients with rare diseases as well as to a list of referred physicians and experts for further assistance. In addition, they deemed information on possibilities of exchanging experiences with other health professionals as well as medical education and training in the field of rare diseases necessary. The health care professionals also placed importance on research (eg, existing studies concerning disease progression). All the health care professionals stressed the importance of patient organizations and self-help groups. We verified the results of the interviews with the doctors in a Delphi survey.

We then used these information needs to further develop the ZIPSE information portal by placing these main information areas prominently on the ZIPSE start page, as well as by integrating them in the layout of the hit list display. Information on registered websites is assigned to these topics so that users can easily search those information topics. Clearly understandable icons, which are displayed on the hit list, indicate what information each individual information website covers.

Quality Criteria for Websites on Rare Diseases

Overall, we identified 9 criteria catalogs and guidelines with recommendations for high-quality health information on the internet from a literature review. A total of 304 single items were extracted, which were reduced to 163 different criteria. Considering the large number of websites on rare diseases, quality criteria for the ZIPSE portal could not refer to the accuracy of all information offered, but to the quality of the information as well as of the preparation of information and of the website. Therefore, we selected criteria to assess how, by whom, and based on which sources the offered information had been collected; how data safety was to be addressed; and how users could contact the website operator. In a workshop with several experts from the field of medicine regarding high-quality online information, the conceptual map comprising 163 different criteria was reduced to a catalog containing 13 criteria, which was used for assessing information websites (Textbox 1). Among others, these criteria included data on the creation process, authors, sources, as well as creation and updating, data security, and declaration of evidence. Some of the criteria could be labeled as "essential criteria" (creation and updating date, data security, imprint, and contact information). Only if these essential criteria are fulfilled, a website will be displayed in the quality assured area of the portal. A criterion containing more than 1 term is deemed to be met when at least 1 term may be considered to be fulfilled. Websites that do not meet all essential criteria will be linked in a separate area. Users can actively request those, but we have to confirm that these websites do not meet the essential quality criteria. We published a detailed description relating to the adoption of quality criteria for websites providing medical information on rare diseases elsewhere [21].

We transferred all the identified quality criteria into a Web-based questionnaire that can be filled online either by the providers of information themselves or by the ZIPSE editorial team. Moreover, we conducted a comprehensive research on existing websites on rare diseases. We identified several hundred websites including those of patient organizations, research institutes, and care facilities and transferred them into a database containing information on the URL, the website provider, and the diseases. Subsequently, we contacted the website provider with a request to register or the editors of the ZIPSE portal registered their information themselves. The information websites were then visible and saved in the administration area of the portal's home page. When website providers registered themselves, the editors of the ZIPSE portal reviewed all information for accuracy and integrity. If necessary, we corrected or completed data. Completely revised information websites that met the essential criteria were then activated, after which they were visible to people searching for related information in the hit list. Nonquality assured information websites were linked to a downstream area.

Technical Implementation and Usability Tests

We set up a webpage on which we placed the basic developed framework of the ZIPSE portal [19]. During the course of the project, we added and evaluated various services, including a disease-specific search function as well as filter options. Through these features, users could search for information on a specific disease and filter search results by topic, information provider, or website features. Moreover, an administration interface was activated. In this interface, all data stored in the system (addresses, contact persons, information on the websites, and its quality aspects) could be managed. Thus, the quality of linked websites could be checked and documented recurrently.

To check whether the information paths, which were developed earlier, suited the target group's specific needs, we conducted focus groups as well as usability tests. Initially, we created an extensive presentation to provide patients with rare diseases and their relatives an overall picture of the portal. Within the framework of focus group discussions, the participants reported high satisfaction regarding clarity, functionality, and comprehensibility. Nevertheless, they reported some points for improving the layout, such as the structural arrangement of the start-up page as well as the display of the hit list, among others. The results directly contributed to the further development and optimization of the ZIPSE portal. Elements on the home page, which were less important to the testers such as the offer to recommend or register a website, can now be found at the bottom of the start-up page, whereas main information areas as well as a mapping of care facilities were placed at a more prominent location. Additionally, new, self-explanatory pictograms for the hit list were created. In the usability tests with patients and physicians, it followed that several aspects could be revealed, which we subsequently revised, including a larger representation of the search field, a clearer presentation of the filter options, and an unambiguous representation of icons and images.

Textbox 1. Zentrales Informationsportal über seltene Erkrankungen (ZIPSE) quality criteria.

Creation process

- Do you perform systematic (literature) research for information creation on your home page? If yes, please describe this process.

- Are experts involved in information creation? If yes, which?

- Is the process of building information on the website documented? If yes, what does this documentation look like? (Please describe)

- Do you illustrate the information building process for your users? If yes, please describe the presentation and name the respective Uniform Resource Locator (URL).

Authors

- General information (names and qualifications) about the authors has been mentioned.

- Other persons, who contributed to developing information, are mentioned.

- Contents authored by users have been labeled and equipped with a user name.

Sources

- Do you provide self-created information?

- If no, do you mention external sources?

Creation and updating (essential criterion)

- The creation date of the information has been mentioned.

- The updating date of the information has been mentioned.

Data security (essential criterion)

- By means of a privacy policy, do you inform the user about the usage, storage, and disclosure of personal data?

- Do you inform the user in a prominent position about the storage of personal data for internal usage (eg, research) with an analysis tool? Does the user have the option to disagree?

- Does the user need to agree actively to the disclosure of personal data to third parties?

Declaration of the evidence

- Is all medical information evidence-based, whereby it is discernible on which basis points are made (eg, studies and expert statements)?

- Do you show the user references to limits of the evidence respectively name more evidence needs?

Marking of conflicts of interests

- Advertisements have been marked as such clearly.

- Sponsors have been named.

- Targets and purposes of the home page have been published clearly (eg, commercial interest).

- The funding (except from self-financing) source has been published.

- Conflicts of interests have been declared.

Consideration of target group

- Information is target-group specific.

- It is discernible to whom the information is addressed (eg, patients or doctors)?

Evaluation

- An archive of former or changed contents exists.

- The accuracy of all the information has been checked consistently.

Review process

- Do you have an internal review process (content quality assessment) for the evaluation of the contents?

- If yes, please describe it.

Characteristics of the website (low-barrier)

- Did you check the website for accessibility through a Barrierefreie Informationstechnik-Verordnung-Test (better: barrier-free information technology regulation test?)? If yes, how many points has the website achieved on this test?

- Is the font size of the website adjustable?

- Do you consider persons with color deficiency in your coloration?

- Can the main menu be accessed without a mouse?

- Is the information available in a simple language (eg, according to the rules of the network simple language)?

- Is the information website available in several languages?

- It is possible to subscribe to a newsletter?

- Is the information available in a printable version?

- Are multimedia contents available (eg, videos and photos)?

Imprint (essential criterion)

Does the imprint contain the following information:

- Name and address of the publisher

- Email address of the publisher

- Declaration of the commercial register, the register of associations, etc, in which the provider is registered, and the respective registration number)

Contact (essential criterion)

- Users can provide feedback or contact the operator.

- A contact sheet is easy to access.

Figure 1. Layout of the Zentrales Informationsportal über seltene Erkrankungen (ZIPSE) start-up page.
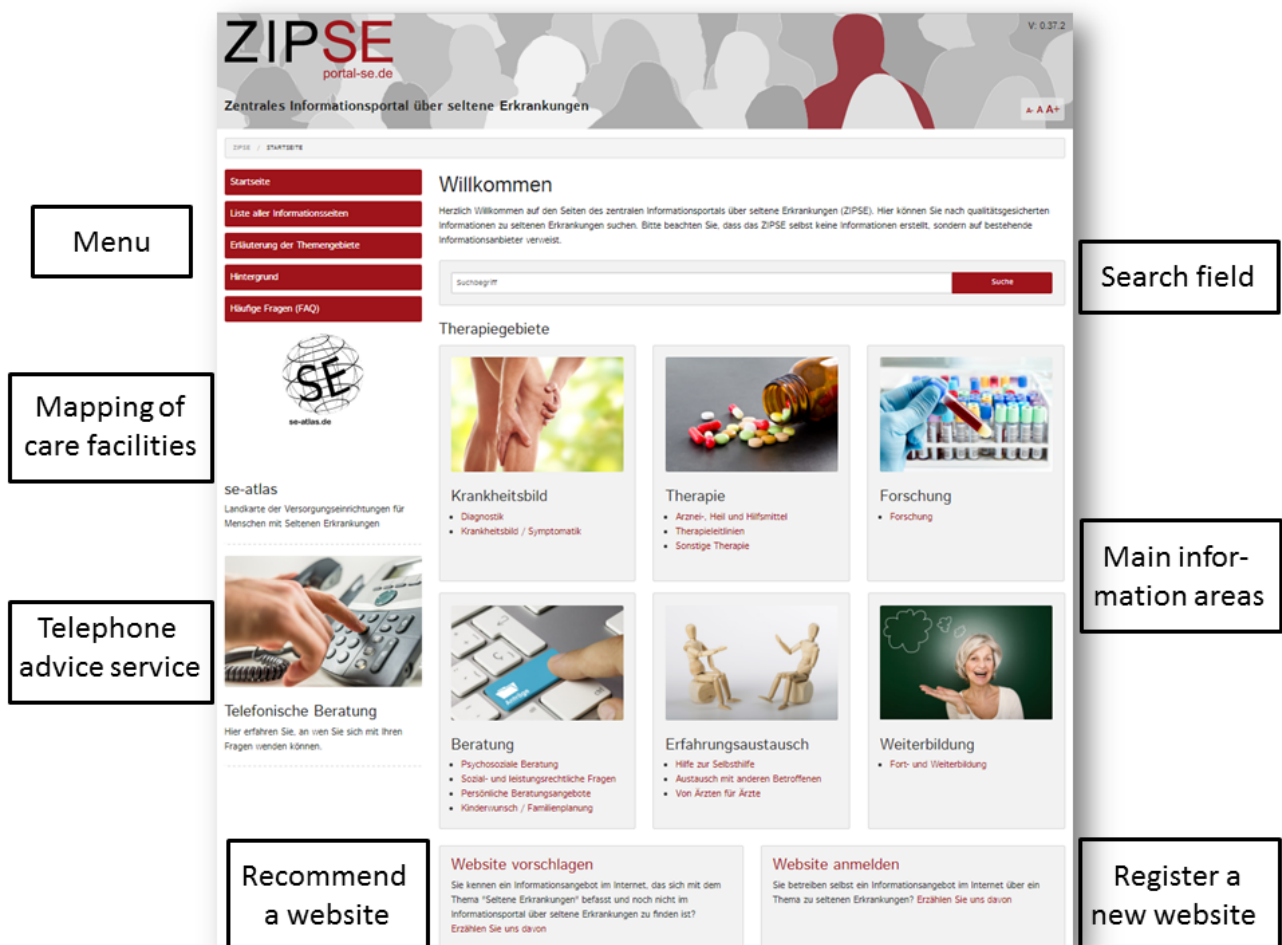
Figure 2. Layout of the Zentrales Informationsportal über seltene Erkrankungen (ZIPSE) hit list page.
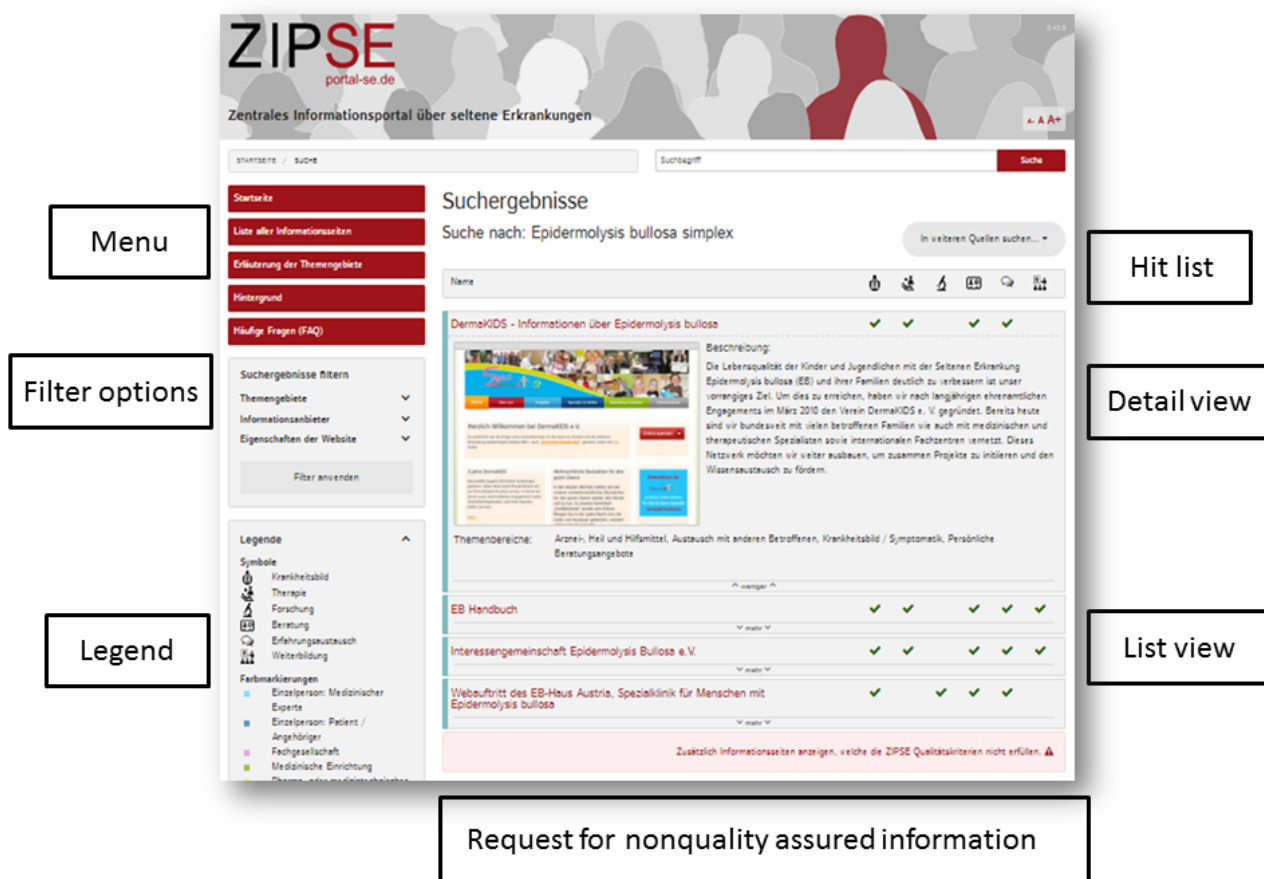
Prototypical Implementation of the Central Information Portal on Rare Diseases

As a result of the procedure described above, we created a functioning information portal. Figure 1 shows the structure of the ZIPSE start-up page. Below the ZIPSE header, users can find the search field in which they can conduct a disease-related search. The menu is displayed in the upper left corner, under which a link to the se-atlas, a mapping service for care facilities on rare diseases, as well as information about telephone advice has been provided. At the bottom of the website, users can find the option to either propose the addition of an information website on rare diseases by providing its name and contact persons, or to register themselves in case they operate a website on a rare disease. Above this option, a selection of different information areas of particular importance regarding the needs identified earlier has been displayed prominently.

When searching for a disease using the search field, a list of linked information websites appears (Figure 2). In this list, all the relevant websites on that specific disease, which have been registered and reviewed positively regarding the essential quality criteria, are presented alphabetically. Next to the name of each information website, an overview of the information areas covered by each site appears (represented by green checkmarks). Moreover, on the left side, users can filter all hits regarding further information areas (which might not have been considered directly in the hit list, but still are relevant), the type of provider, as well as characteristics of the website (such as accessibility and multilingualism). Clicking on one of the matches produces a detailed view of the website. This includes a screenshot of the webpage's start-up page, as well as a short description of the contents of this site. The users then have the option to be forwarded to the website by clicking on its image. Information websites that do not meet the essential quality criteria can be requested at the bottom of the hit list. By clicking the corresponding button, these are shown in the hit list and are clearly marked.

Discussion

Principal Findings

During the course of the project, we developed and implemented a prototype of a central information portal on rare diseases that fulfills the needs of patients, their relatives, physicians, and other health care professionals. Currently, 720 information websites have registered on the portal. About half of the websites meet the essential quality criteria, whereas the other half can be found in the nonquality assured area of the portal. A total of 239 websites refer to genetically caused diseases (239/720, 33.1%). Another 92 websites focus on neurological conditions (92/720, 12.7%). This is followed by 72 websites on neoplastic diseases (72/720, 10.0%) as well as 40 websites on developmental defects during embryogenesis (40/720, 5.5%). All other disease groups are in the lower single-digit percentage range.

The information needs identified through qualitative interviews were in line with different international studies [14-17] as well as with information offerings on a random sample of existing websites on rare diseases, selected from the ZIPSE database. On the ZIPSE portal, users can search for information on rare diseases from this central point of access. There also lies the crucial benefit over other online offerings on rare diseases, which are often widely dispersed over the internet. To switch from one source to another can be challenging for information seekers. ZIPSE combines all the varying kinds of information websites at one central point. Moreover, all the available information on ZIPSE can be easily filtered by topics that have been shown to be particularly important or by the type of provider as well as by characteristics of the website. Thus, the compiled high-quality information will be more accessible to the interested or affected people.

To offer added value to people with rare diseases, continuous maintenance and optimization of the information portal and its structures and services is of utmost importance. Not only must existing links and contents be kept up to date, but other information websites, including websites from English-speaking countries, must also be identified and integrated within the portal. Especially for people with diseases for which little information is available in German, such information in English could be very useful. Therefore, we will maintain, update, and continuously develop ZIPSE. However, to sustain the availability of ZIPSE, a major challenge for the near future would be to find funding sources. To make sure that all work continues, we are constantly developing different solutions for sustainable funding after the end of this publicly funded project.

By compiling information on rare diseases at one central point of access, in the future, people can identify gaps in knowledge about specific diseases more easily. One can infer that there is insufficient information on all rare diseases, especially on very rare diseases, where only little research has been carried out owing to financial restrictions as well as small numbers of available patients. Without research, no knowledge and information can be generated. This explains why for many (very) rare diseases only little or no information is available online. Addressing these knowledge gaps could be an important task for future studies.

Our concept of a central information portal on rare diseases could be useful as a model for other information providers in the field of rare diseases, for the development of similar information systems. Even though there is a range of other information systems providing information on rare diseases to different target groups, this is the first one that was developed by using extensive scientific methods and integrating all target groups in its development. Due to this study's underlying scientific approach regarding the collection of people's information needs and definition of quality criteria, as well as the involvement of patients, their relatives, and physicians at all stages of the project, one can assume a high target group–specific alignment that could be transferred to other systems.

Limitations

Due to the limited financial and personnel resources in this publicly funded research project, some of the ideas regarding the structure and function of the information portal could not be fully developed. These include, for example, the establishment of a newsletter that informs users about newly included information sites on specific diseases or issues when requested. This could be a task for future operators of the website.

Conclusions

Dealing with the various challenges arising from rare diseases has become an important task for most health care systems. Especially, the gaps in knowledge and the uncertain quality of information pose challenges for the establishment of networks of information infrastructures. Even though there is information on many rare diseases, it is often insufficiently known and used due to low visibility. Establishing a central information portal like ZIPSE makes the existing but widely dispersed information accessible to the various groups of people dealing with rare diseases.

For patients and their families, this offers an opportunity for easy access to extensive information on topics that are important to them, such as therapy, social and legal issues, and self-help. For doctors and other medical professionals, the ZIPSE portal can help to accelerate the diagnostic process and improve patient care by providing information on rare disease diagnostics, therapy, and specialized care facilities. Therefore, bundling high-quality information at one central access point can improve people's health care sustainably. In the future, it will be easy to find trustworthy information for people living with a rare disease by using the ZIPSE portal. Furthermore, with reference to professional caregivers, reducing uncertainties in diagnostics and therapy could prevent the overuse, underuse, and misuse of information in the health care sector. Moreover, the ZIPSE portal can help raise awareness about rare diseases in general. One of the current challenges concerning rare diseases is not only missing information but also the lack of awareness about them. Along with closing gaps in people's knowledge, the ZIPSE portal can help sensitize people regarding rare diseases.

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Conflicts of Interest

None declared.

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Abbreviations

BMG: Federal Ministry of Health Germany
ZIPSE: Central Information Portal on Rare Diseases

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Protocol

Development of a Web Portal for Physical Activity and Symptom Tracking in Oncology Patients: Protocol for a Prospective Cohort Study

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Abstract

Background: Significant benefits accrue from increasing physical activity levels in people with a history of cancer. Physical activity levels can be increased using behavioral change interventions in this population. Access to Web portals and provision of activity monitors to provide feedback may support behavior change by encouraging patient engagement in physical therapy. The Web portal evaluated in this study will provide a system to monitor physical activity and sleep, for use by both clinician and patient, along with symptom and health-related quality of life tracking capabilities.

Objective: The aim of this study was to outline a protocol for a feasibility study focused on a Web-based portal that provides activity monitoring and personalized messaging to increase physical activity in people with cancer.

Methods: Using a longitudinal cohort design, people with cancer will be serially allocated to 3 intervention cohorts of 20 participants each and followed for 10 weeks. Cohort 1 will be provided a wearable activity monitor and access to a Web-based portal. Cohort 2 will receive the same content as Cohort 1 and in addition will receive a weekly activity summary message. Cohort 3 will receive the same content as Cohorts 1 and 2 and in addition will receive a personalized weekly coaching message. Feasibility of the use of the portal is the primary outcome.

Results: Results are expected in early 2018. Outcome measures will include goal attainment and completion rate.

Conclusions: This study will provide information about the feasibility of investigating eHealth initiatives to promote physical activity in people with cancer.

Registered Report Identifier: RR1-10.2196/9586

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Introduction

Physical Activity and Cancer

There is consistent evidence that exercise prescribed during or following completion of cancer treatment is safe and feasible and reduces clinically important symptoms and side effects, including fatigue, low mood, and loss of muscular strength and aerobic fitness [1-3]. In addition, evidence is emerging that exercise may positively impact treatment delivery, such as improvements in chemotherapy completion rates, number of dose reductions, as well as decreased cancer recurrence rate and improved overall survival in some cancers [2,3]. Despite this evidence, achieving behavioral change in cancer populations in relation to exercise has been challenging [4]. Physical activity levels typically decline significantly during intensive cancer treatments, such as chemotherapy and radiation therapy, and often do not return to prediagnosis [5] or minimum recommended levels [6].

eHealth and Web-Based Portals

eHealth can be broadly defined as the integration of devices, communication, and data in health care [7]. The use of eHealth tools, such as Web portals, wearable activity trackers, and personalized text and email messaging, may increase the capacity for delivering individualized, scalable, and cost-effective physical activity–based behavioral change initiatives in this population.

Research involving patients with a history of cancer indicates that most have positive attitudes toward the use of eHealth methods in their management and care of cancer [8]. The use of Web portals by patients with a chronic condition such as cancer is a growing area of eHealth research. Web portals can have many uses including patient access to personal medical records, appointments, medications, communication with health professionals, and decision support tools [9-13]. The use and application of Web portals provide opportunities to improve physical activity behavior change. Patients with access to Web portals tend to have greater engagement in their treatment, lower treatment distress, increased treatment satisfaction, and improved communication with health professionals [9-13].

Web-based methods such as Web portals also provide a new method to record, track, and relay patient-reported outcome (PRO) measures to health professionals involved with patient care. Symptom tracking and reporting using PRO measures have been shown to improve patient outcomes in cancer care [14]. Historically, paper- or phone-based interactive voice response systems have been used [15,16]. The novel approach of using a Web portal for the collection and communication of PRO may provide a more effective platform for health care professionals to facilitate long-term behavior change in cancer survivors.

Wearable Activity Trackers

Accelerometers (or activity trackers) are small, lightweight devices worn on the wrist or hip. Activity trackers have been used extensively in clinical research of physical activity [17]. Recently, they have become more available to consumers with the release of relatively low-cost and accessible products. Commercially available accelerometers have been validated as an accurate measure of physical activity and sleep metrics [17,18], including models from Misfit, Fitbit, and Garmin. In people with cancer, accelerometers provide a reliable and feasible method to measure, monitor, and encourage physical activity [18]. A major issue when using commercially available activity trackers in clinical practice is that individual patient data are not readily available to health professionals involved in their care. Web portals can provide a mechanism for data transfer through an application programming interface that supports interaction between software components, giving both patients and health care professionals access to real-time data.

Personalized Messaging

The use of email and SMS (short message service) text messaging is ubiquitous in the general population. The use of SMS text messaging as a behavioral change intervention, including personalized messaging, has emerged as a promising approach to promote positive behavior change [19]. Personalized messages (PMs) are often sent daily or weekly, aiming to improve lifestyle behaviors including improving physical activity levels, sleep quality, and nutrition habits. PMs are likely most effective when tailored to each patient rather than generalized to broader audiences [20,21]. The intended benefit of regular PMs is to elicit long-term and sustainable behavior change.

Our study aims to evaluate the feasibility of a dual-facing (patient and clinician) Web portal, which incorporates synchronized data from activity trackers, symptom management, and PMs as a method of monitoring and improving care for people with cancer who attend an Australian comprehensive cancer care center.
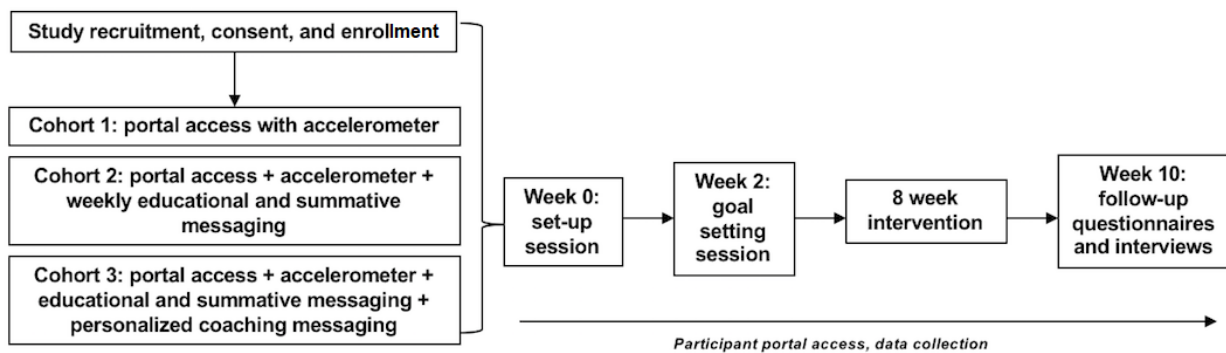
Methods

Study Design

The study will be a prospective longitudinal cohort design. Participants will be enrolled serially into 3 successive cohorts: the first 20 participants enrolled were entered into Cohort 1, the second 20 into Cohort 2, and the final 20 into Cohort 3. No form of random allocation will be used.

Cohort 1 will be provided Web portal access with an accelerometer for 10 weeks. Cohort 2 will be provided Web portal access, accelerometer, and an additional weekly, automated summary message that details average scores over the last week, along with specific educational content such as information on cancer-related fatigue and nutrition. Cohort 3 will receive the content received by Cohort 2 and additional personalized behavioral change messaging from an accredited exercise physiologist (EP). Figure 1 shows the schematic research design.

Participant Inclusion and Exclusion Criteria

A convenience sample of patients registered with the cancer care center, either currently undergoing treatment or who have completed treatment within the last 6 months, will be invited to participate in the study.

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Figure 1. Schematic summary of the study.

Figure 2. Example of a patient-facing Web portal home page and virtual diary.

Participant inclusion criteria will be as follows: (1) aged 18 years or older, (2) have an Eastern Cooperative Oncology Group Performance Status score of 0 to 2, and (3) have smartphone and Internet access readily available.

Participants will be excluded if they (1) are unable or have limited ability to speak English and (2) have any condition that would compromise their ability to understand the participant information or give informed consent.

Development of the Web Portal

The Web portal was developed with an industry partner (Springday Pty Ltd), under a collaborative research agreement.

An initial focus group involving patient consumer representatives (n=2) and clinicians (n=8) working in oncology was organized to obtain feedback on user experience, content, and design. During the focus group, a draft design was discussed, and suggested improvements were documented and incorporated where possible.

There are 2 main components of the Web portal: (1) the participant interface and (2) the clinician interface. The participant interface provides a website for individuals to synchronize data from their personal activity tracker and view their activity and symptom data (Figure 2). It also provides access to a Web-based library containing information about cancer, cancer treatment, and the benefits of adopting healthy lifestyle behaviors, including better nutrition, exercise, and sleep habits. Links to supportive networks and government-supported cancer information websites will be provided via the Web portal.

The clinician interface, also called the *coaching dashboard*, provides clinician users with an overview of all participants under their care. It summarizes participant demographics, activity tracker, and symptom trends both individually and overall (Figure 3). PRO measure data are available, with data trends visible. Activity tracker information is securely synchronized from the participant's smartphone to the Web portal every 30 min using an application programming interface.
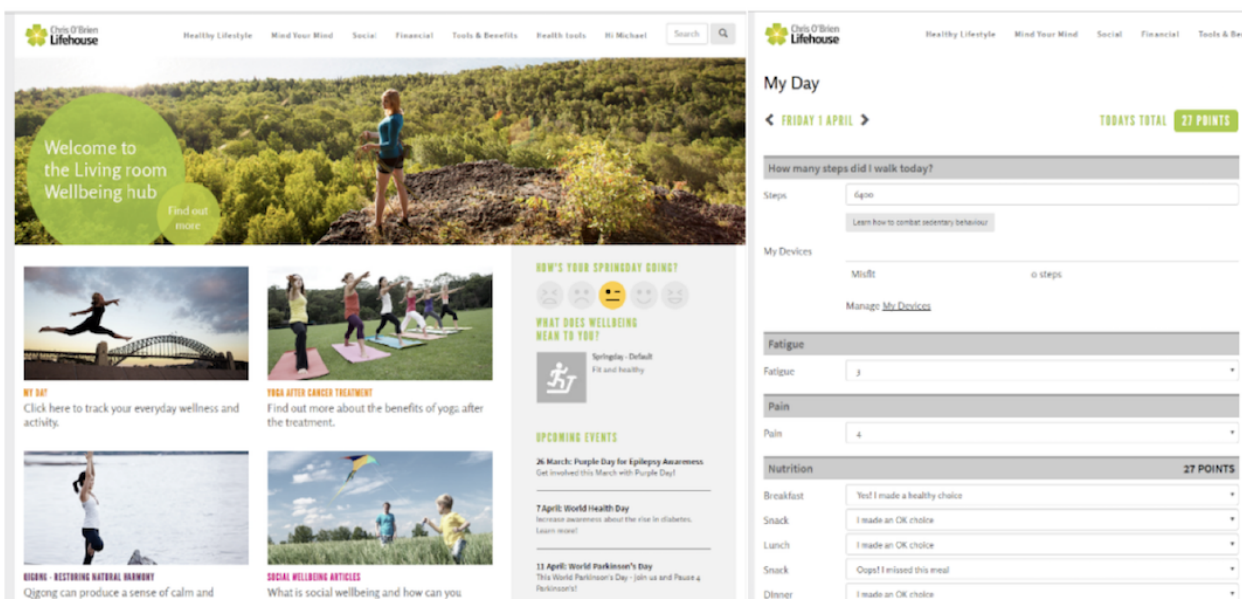
Figure 3. Example of an individual data snapshot in clinician facing "coaching dashboard".
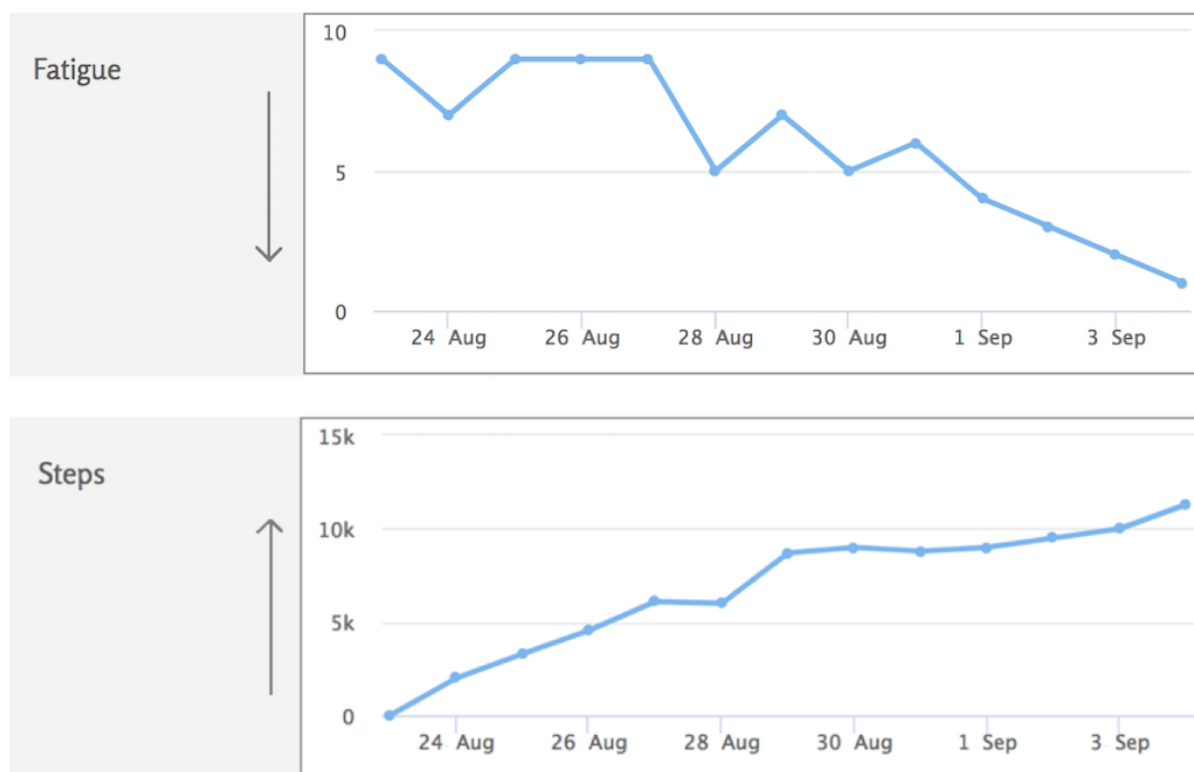
Activity and Sleep Tracker

The study will use the commercially available Misfit Shine activity monitor. Misfit Shine was chosen because of its 3- to 6-month battery life, Bluetooth synchronization capability, and water-resistant characteristics. This device has been validated as a physical activity measurement instrument in healthy populations [22]. Participants enrolled in the study are able to bring their own device if they currently own one from the Misfit, Garmin, or FitBit product ranges as the Web portal has the capacity to synchronize data from these devices.

Recruitment Procedure

There will be rolling serial recruitment into each of the 3 cohorts. Once 20 participants have been recruited for Cohort 1, recruitment will then start for Cohort 2. After 20 additional participants have been recruited for Cohort 2, recruitment will start for Cohort 3. Eligible patients will be identified by either a clinical nurse consultant, physical therapist, or a supportive care and integrative medicine specialist. The clinician will provide a written participant information sheet to potentially eligible participants. Potential participants consenting to be contacted will be screened to confirm eligibility and will be provided verbal information about the study. Participants will be registered into the study after signing the informed consent form during their individual orientation session. Due to the nature of working with a population who are undergoing intensive cancer treatment, a slight attrition is expected to occur in each cohort.

Intervention

The intervention will include evidence-based components of education, goal setting, monitoring, feedback, and motivation as described by Michie et al [23]. It is a behavioral change intervention, primarily focused on remote symptom monitoring and increasing physical activity levels. The intervention is divided into 3 major components covered in individual sessions: (1) orientation, (2) goal setting, and (3) individual messaging. All 3 cohorts will complete sessions 1 and 2, and additionally, Cohort 2 will receive automated summary messages, and Cohort 3 will receive individualized coaching messages.

Orientation Session

An initial, 30-min, one-to-one session will be conducted in person with the participant and an EP. The EP will orient the participant regarding the use of the activity monitor and the Web portal. The participant will be involved in entering their demographic data into the Web portal, downloading the MisFit Shine mobile app, and synchronizing this device with the Web portal. An information pack including the Misfit Shine user manual and instructions for the Web portal will be given to each participant.

Goal Setting Session

Each cohort will have an initial 2 weeks of Web portal access to determine baseline activity levels. Following this initial data collection phase, a 15-min goal planning session will be conducted with an EP either face-to-face or by telephone. This session will aim to set a daily step goal for each participant to achieve over the duration of the study, typically 10% greater

than the participant's median daily value over the last 2 weeks. Step goals will be capped at 15,000 steps per day.

Web Portal Access

Participants will have access to the Web portal for 8 weeks after the goal setting session, 10 weeks in total. During this time, data, both from the activity tracker and those which are manually entered, will be collected and will be accessible for both the participant and study investigators. Participants will be asked to wear the activity tracker for the duration of the study and synchronize their device daily. Participants will able to track their fatigue and pain scores daily on the Web portal. These symptoms will be rated on a Likert scale from 0 (none) to 10 (worst imaginable) using a drop-down menu.

Personalized Messaging

Following the goal setting session in week 2, the Web portal will provide 2 types of coaching messages to participants in Cohorts 2 and 3 through weekly emails. Cohort 2 will receive a summative message providing participants with a summary of their exercise history, sleep duration, and an overview of their fatigue and pain scores.

Cohort 3 will receive the same general summative message as Cohort 2 as well as weekly health coaching messages that will be tailored based on the participant's progress over the last week. This will also take into consideration messages received from the participant, which may include information such as barriers, goals, and treatment status.

Technical Support

Participants will have access to technical support for the duration of the study. This includes telephone and email support with the study coordinator during standard business hours on week days.

Study Procedures

Table 1 depicts the investigations and timings from preregistration to week 10. At the first face-to-face session, baseline questionnaires will be completed on the Web portal. The following validated PRO measures will be used:

1. Edmonton Symptom Assessment Scale: An 18-item, patient-rated symptom visual analogue scale developed for use in assessing cancer-related symptoms [24].
2. Functional Assessment of Cancer Therapy-General: It is a 27-item compilation of general questions divided into 4 primary health-related quality of life (HRQoL) domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. It is considered appropriate for use for patients with any form of cancer [25].
3. Cancer Behavior Inventory-Brief version: This self-efficacy scale [26] will also be given to the participants to complete.

An additional study-specific feedback questionnaire will be remotely administered via a Web survey to assess the following: (1) participant satisfaction with the device and Web portal, (2) perceived appropriateness of the device and Web portal, (3) ease of use of the Web portal, (4) intent to continue using the device and Web portal, (5) device and Web portal technology issues, (6) personal technology use, (7) telehealth usability, and (8) general feedback.

Semistructured Interviews

Qualitative, semistructured interviews will be conducted with participants to capture, in depth, their experience of the intervention. This method enables the researchers to explore in-depth insights into the experiences and perspectives of individual participants. Interviews will be conducted either face-to-face or via telephone by an individual not involved in delivering the intervention or the participant's clinical care. Each interview will be audio-recorded and transcribed verbatim. The transcripts will be coded and themes will be identified using a thematic approach to analysis in a framework structure. Interviews will be conducted with consenting participants in each cohort of the study and will continue until saturation of themes has been achieved.

Data Management

Paper copies of signed consent forms will be stored securely at the participating site. Data synchronized from the activity monitor or entered manually will be stored on the Web portal Web server. The participant Web portal uses HTTPS to encrypt traffic; database servers employ encryption at rest; and users have individual passwords. During the data analysis phase, participant Web portal data will be extracted and stored on a secure, customized electronic Research Electronic Data Capture (REDCap) database housed on a secure server. REDCap is a browser-based software for capturing clinical and translational research data created by the Vanderbilt University. Access to the server will be restricted to study investigators only and via individual passwords.

Primary and Secondary Outcomes

The primary outcome of interest is the feasibility of the program. The intervention would be deemed feasible if a compliance rate of >70% is observed.

Compliance is defined based on 2 measures:

1. Log-ins: a patient is defined as compliant if they have more than 2 log-ins over the 10-week study period.
2. Questionnaires: a patient is defined as compliant if they complete the follow-up questionnaire at week 10.

For the study to be deemed feasible, >70% of the participants need to comply with both criteria, not just one.

The secondary objectives of the study are as follows:

1. To describe goal attainment; the number of individuals who are eligible and take up the program; the rate of program completion; satisfaction with the intervention; self-efficacy related to change in lifestyle factors; and clinical changes including symptom and HRQoL scores
2. To analyze Web portal data to determine median daily step count, weekly email engagement (Cohorts 2 and 3), and number of PMs sent (Cohort 3)
3. To compare accelerometer data from the first week (week 1) and final week (week 10).

Table 1. Data collection schedule. Checkmarks indicate time points when data were collected.

Data collection	Preregistration	Baseline	Week 2	During the intervention	Week 10
Eligibility check	✓				
Consent		✓			
Demographics		✓			
Goal setting			✓		
Functional Assessment of Cancer Therapy-General		✓			✓
Edmonton Symptom Assessment Scale		✓			✓
Cancer Behavior Inventory-Brief version		✓			✓
Pain score (0-10)			✓	✓	
Fatigue score (0-10)			✓	✓	
Activity tracker data			✓	✓	
Web portal usage data				✓	
Adverse events				✓	
Participant survey					✓
Interviews					✓

Data Analysis

Baseline demographics will be summarized as frequency (%) for categorical variables and as mean (SD) or median (interquartile range, IQR) for continuous variables, depending on the distribution. The number of compliant participants within each cohort will be summarized as frequency (%). The number (%) of patients who attained their step goal will be summarized weekly and by cohort, along with the median number of weeks where goals were attained.

The daily step count will be summarized at week 1 and week 10 for each cohort as mean (SD) or median (IQR). The mean difference between week 1 and week 10 will be displayed alongside the corresponding 95% CI. Data will be analyzed on the days the accelerometer was worn, defined as more than 250 steps.

Quality-of-life questionnaires will be summarized as median (IQR) or mean (SD) at the initial and week 10 visit for each cohort group. The mean difference between time points will be displayed alongside the 95% CI.

The frequency (proportion) of opened emails will be summarized for Cohort 2 and Cohort 3 by each week of the study, and the number of PMs opened by Cohort 3 will be summarized as frequency (%).

The number of symptoms reported will be used to investigate the association of baseline characteristics with engagement in the study. A Mann-Whitney U test will be used to compare the number of symptoms between categorical variables, and Spearman correlation will be used to investigate the association with continuous variables.

Ethics

Permission to conduct this study has been granted by the Royal Prince Alfred Hospital Human Research and Ethics Committee (X16-0051). All participants will provide written informed consent, and the study will be conducted in accordance with the Declaration of Helsinki and applicable national guidelines.

Results

The project was funded in 2016, and enrollment was completed at the end of 2017. Data analysis is currently under way, and the first results are expected to be submitted for publication in 2018.

Discussion

Reduced physical activity levels during cancer treatment can lead to increased symptom burden and consequently reduced quality of life. There is no single solution to facilitate positive behavior change across a population of people with cancer in active treatment; however, the innovative use of technology may benefit a proportion of the population. Patients with cancer who have tertiary education, who are undergoing intensive treatment, and those who report reduced HRQoL express a more positive perception of and openness to use of Web portals [8,27]. Despite an overall positive perception of eHealth interventions, there are varying perceptions of their usability from both patients and clinicians, although benefits to self-management and outcomes have been demonstrated [8,9].

It is acknowledged that this study will recruit a heterogeneous patient sample, with various tumor types and treatment stages represented. However, the decision to include a heterogeneous sample was deemed appropriate for a feasibility study and is also pragmatic for recruiting the required sample within a short time frame as well as the generalizability of the findings. Where patient numbers are sufficient, we will explore the impact of the intervention on specific tumor groups, stages of disease, and point in the cancer treatment trajectory to inform the design of any future efficacy trials.

The utility of Web portals for clinicians and clinician-patient relationships is an important benefit of such systems. This study does not include data review or interactions with medical specialists; rather, it will be limited to an exercise professional. Depending on feasibility, future iterations will include such components.

Determining the feasibility of the intervention is the major objective of this study. The inclusion of qualitative interviews strengthens the study and will help to guide future development of the system and studies. User-designed health systems have been shown to increase functionality, specificity, and uptake [28].

Results from this prospective cohort study will add to the body of evidence surrounding the use of eHealth initiatives to facilitate physical activity behavior change and symptom tracking in people with cancer. It is anticipated that the results of this pilot will inform the design of a future randomized controlled trial that will be adequately powered to assess clinically relevant outcomes.

Acknowledgments

Conflicts of Interest

None declared.

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Abbreviations

EP: exercise physiologist
HRQoL: health-related quality of life
IQR: interquartile range
PM: personalized message
PRO: patient-reported outcome
REDCap: Research Electronic Data Capture
SMS: short message service

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Protocol

Implementation and Effects of Risk-Dependent Obstetric Care in the Netherlands (Expect Study II): Protocol for an Impact Study

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Abstract

Background: Recently, validated risk models predicting adverse obstetric outcomes combined with risk-dependent care paths have been made available for early antenatal care in the southeastern part of the Netherlands. This study will evaluate implementation progress and impact of the new approach in obstetric care.

Objective: The objective of this paper is to describe the design of a study evaluating the impact of implementing risk-dependent care. Validated first-trimester prediction models are embedded in daily clinical practice and combined with risk-dependent obstetric care paths.

Methods: A multicenter prospective cohort study consisting of women who receive risk-dependent care is being performed from April 2017 to April 2018 (Expect Study II). Obstetric risk profiles will be calculated using a Web-based tool, the Expect prediction tool. The primary outcomes are the adherence of health care professionals and compliance of women. Secondary outcomes are patient satisfaction and cost-effectiveness. Outcome measures will be established using Web-based questionnaires. The secondary outcomes of the risk-dependent care cohort (Expect II) will be compared with the outcomes of a similar prospective cohort (Expect I). Women of this similar cohort received former care-as-usual and were prospectively included between July 1, 2013 and December 31, 2015 (Expect I).

Results: Currently, women are being recruited for the Expect Study II, and a total of 300 women are enrolled.

Conclusions: This study will provide information about the implementation and impact of a new approach in obstetric care using prediction models and risk-dependent obstetric care paths.

Trial Registration: Netherlands Trial Register NTR4143; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4143 (Archived by WebCite at http://www.webcitation.org/6t8ijtpd9)

Introduction

Perinatal mortality plays a pivotal role in the quality assessment of perinatal care [1]. In developed countries the main causes of perinatal mortality are small-for-gestational-age infancy (SGA), preterm birth (PTB), and asphyxia [2,3]. Pre-eclampsia (PE) is an important cause for both SGA and induced PTB [4]. Risks of asphyxia and birth injuries are increased among infants that are large-for-gestational-age (LGA) [5], which in turn is strongly associated with gestational diabetes mellitus (GDM) [6]. Thus, PE, GDM, PTB, SGA, and LGA are all directly or indirectly related to perinatal mortality.

A number of interventions have shown to be effective in the prevention of adverse pregnancy outcomes, such as calcium suppletion and low-dose aspirin treatment in case of PE [7-9], adequate management of GDM [5,10,11], and progesterone administration in women at risk of spontanous PTB [12]. Besides calcium supplementation, most of these interventions are not suitable for all pregnant women, because of either possible adverse effects, patient burden, or costs. Early prediction of obstetric risks may therefore help health care professionals in designing intervention strategies based on women's individual risks.

Recently, we performed an external validation study of first trimester prediction models predicting the risk of PE, GDM, PTB, SGA and LGA (the Expect Study I) [13,14]. The Expect Study I identified clinically useful prediction models for PE and GDM. The Limburg Obstetric Consortium (LOC), midwives and gynecologists of the southeastern part of the Netherlands developed care pathways, for example, basic antenatal care for women at low risk and additional risk-dependent care for women with elevated risks of PE, GDM, PTB, SGA, or LGA. The LOC agreed to implement the risk models predicting PE and GDM, in order to identify women at increased risk of these outcomes, and to offer these women risk-dependent care.

The current protocol describes the design of a multicenter prospective cohort study (Expect Study II) evaluating the implementation progress of using these prediction models combined with tailored care paths for PE and GDM.

The primary aims of the Expect Study II are to measure adherence to the new risk-dependent care guidelines by health care professionals and compliance of pregnant women who received recommendations. The secondary aims are to evaluate its impact upon patient satisfaction and cost-effectiveness. Secondary aims will be studied by comparing these outcomes of the Expect II cohort with the Expect I cohort.

Methods

Study Design and Recruitment

In April 2017, the Expect prediction tool, was introduced. The Expect prediction tool was developed to enable individual risk assessment during early pregnancy regarding the risks of PE, GDM, PTB, SGA, and LGA. Validated models selected by the LOC to predict PE and GDM have been incorporated into this tool (unpublished study submitted by Meertens et al, January 2018). Risk assessment of spontaneous PTB, SGA and LGA is achieved using the revised LOC guidelines [15]. For nulliparous women, the prediction tool comprises 14 variables concerning anthropometric data, relevant medical history, and family history. For multiparous women the tool enquires 6 more variables, all concerning the women's obstetric history.

The Expect prediction tool is a Web-based form which calculates the estimated risk profiles. This tool was made available for health care professionals via the Expect study website for implementation in daily obstetric care. Besides the estimated risks of adverse pregnancy outcomes, the tool provides recommendations for tailored antenatal care based on personalized risks (ie, risk-dependent care). In addition, patient information brochures relevant to the patient's risk profile will be automatically generated. The health care professionals can use this tool during one of the pregnant woman's antenatal visits before 16 weeks of pregnancy. Using a shared decision approach, the appropriate risk-dependent care path with corresponding preventive measures and check-ups will be selected.

In order to implement risk-dependent care successfully, midwives and gynecologists are encouraged to use the Expect prediction tool by representatives of the LOC. The Expect prediction tool is introduced by email to all obstetric health care professionals in the region. Furthermore, oral presentations will be given at every hospital and at local midwifery meetings. Additionally, the hospitals and midwifery practices are contacted regularly by phone and in person to evaluate the Expect prediction tool.

The midwives and gynecologists play a central role in enrolling pregnant women into the Expect Study II, by asking women whether they are interested in receiving further information about participating in the Expect Study II. Almost every pregnant woman is eligible for our study. The exclusion criteria are (1) maternal age <18 years, (2) documented multiple pregnancy, and (3) ≥16 weeks of gestation at intake. The eligibility criteria are identical to those of the Expect Study I cohort [13]. Eligible women agreeing to participate are asked to give informed consent and to complete 4 Web-based surveys at enrolment, 24 weeks and 34 weeks of gestation, and 6 weeks after due date.

A personal link to the first online survey will be sent immediately after enrolment. If the survey was not accessed or incomplete, 2 automatic reminders will be sent by email at 3-day intervals for surveys one to three and at 6-day intervals for the postpartum survey. In case of non-response, women will be contacted by phone (provided that a correct phone number is available). If women report PTB at the beginning of survey two

or three, they will automatically be redirected to the postpartum survey.

The medical ethical committee of Maastricht University Medical Centre evaluated the study protocol and declared that the study did not fall within the scope of the Dutch Medical Research Involving Human Subjects Act (WMO; METC-17-4-057).

Tailored-Care Paths

The LOC consists of midwives (n=9), gynecologists (n=9), professionals in maternity care (n=2), researchers (n=3), and an independent chairman. They meet four to five times annually and represent the University medical school, midwifery academy, all hospitals, and roughly 80% (n=90) of the midwives of the province. The midwives and gynecologists of the LOC revised the content of obstetric care. We will briefly describe the most important changes regarding antenatal care compared to former care-as-usual which has been observed during Expect Study I. All women will receive basic antenatal care. In the new tailored care paths, recommendations about calcium and vitamin D supplementation are emphasized for all women and an additional ultrasound for fetal growth assessment at 32 weeks of pregnancy is introduced as part of basic antenatal care.

An overview of the care pathways is provided in Table 1. Additional risk-dependent care for women with a mildly elevated risk of PE comprises the recommendation of preventive aspirin treatment, 80-100 mg aspirin daily from 12 weeks up to 36 weeks of pregnancy. Obstetric care for women with a substantial risk of PE additionally comprises of extended blood tests, blood pressure measurements every 2 weeks from 14 weeks up to 40 weeks of gestation, and 2 additional ultrasounds for fetal growth measurements.

Women with a history of GDM are advised to have an oral glucose tolerance test (OGTT) at 16 and 26 weeks of pregnancy. Women with a mildly elevated risk are advised to have an OGTT at 24 weeks of pregnancy. Furthermore, in both cases, women will receive two additional ultrasounds for fetal growth measurements in addition to basic antenatal care.

Outcome Measures and Measurement

The primary outcomes are health care professionals' adherence to key recommendations and compliance of the women involved in the study. Adherence is defined as the proportion of women that actually received the key recommendations they should have received from their health care professional according to the LOC guidelines. Adherence will be analyzed regarding recommendations of adequate vitamin D (yes or no) and calcium intake (yes or no) for all women, preventive aspirin treatment (yes or no) for women with elevated PE risks, and OGTT (yes or no) for women with elevated GDM risks.

Compliance is defined as the proportion of women whom comply with the LOC recommendations they have received (yes, no or partially). Compliance will be analyzed regarding: adequate vitamin D (10 microgram per day) and calcium (1,000 milligram per day) intake, preventive aspirin treatment, and OGTT.

The secondary outcomes are patient satisfaction and cost-effectiveness. These secondary outcomes of Expect Study II will be compared to the outcomes of Expect Study I.

Patient satisfaction will be measured by validated patient satisfaction questionnaires. The Patient Satisfaction Questionnaire Short Form will be incorporated in antepartum surveys two and three. In the postpartum survey, patient satisfaction will be assessed by the Pregnancy and Childbirth Questionnaire (PCQ) [16]. The PCQ is validated for Dutch women who recently gave birth and addresses three topics: women's satisfaction with the health care professional during pregnancy, health education, and satisfaction with the health care professional during labor. Furthermore, Truijens et al showed the PCQ is sensitive to pick up effects regarding patient satisfaction due to simulation-based obstetric team training [17].

In order to perform cost-effectiveness calculations, we will calculate two incremental cost-effectiveness ratios (ICERs). The first ICER expresses the health care costs per one neonatal composite outcome prevented. The neonatal composite outcome is defined as perinatal death within seven days after birth, asphyxia (Apgar score <7 after 5 minutes), admission to a neonatal intensive care unit within 28 days after birth, SGA (birthweight <2.3 weight percentile), and very preterm birth (birth before 32 completed weeks of pregnancy) [13]. The second ICER will express the health care cost per one maternal gained Quality Adjusted Life Year (QALY).

Data Collection

For the primary outcomes, we will use the data collected for the Expect Study II. For the secondary outcomes, when comparing the effects of risk-dependent care with former care-as-usual, the outcomes of the Expect Study II will be compared with the outcomes of the Expect Study I. For this reason, the survey intervals and the questions regarding the secondary outcomes are similar between the two studies.

In the Expect Study II, data will be collected using the Expect prediction tool, comprising women's personal risk profile, and Web-based patient surveys. A structured overview of patient enrolment and data collection for the Expect Study II is shown in Figure 1.

The first survey addresses the following topics: (1) recommendations and information given by health care professionals, (2) women's intention to comply with these recommendations, (3) dietary intake of calcium and vitamin D and sunlight exposure, and (4) vitamin and mineral supplement usage.

The second and third surveys are comparable to each other and will address the following topics: (1) patient satisfaction, (2) women's state anxiety, (3) maternal quality of life, (4) changes in vitamin and mineral supplement usage, and (5) health care resource use.

**Table 1.** Overview of care pathways.

Gestational age (weeks)	Basic antenatal care for all women	Additional risk-dependent care				
		Pre-eclampsia (mildly elevated risk)	Pre-eclampsia (high risk)	Gestational diabetes mellitus	Small or large gestational age infancy	Spontaneous preterm birth
6-10	Intake and risk assessment using the Expect prediction tool and general recommendations (eg, Calcium and vitamin D intake)					
10-12	Confirmation gestational age (crown rump length ultrasound) and blood tests (eg, blood type, hemoglobin)	Low dose aspirin prophylaxis	Low dose aspirin prophylaxis and extended blood tests (eg, renal function)			Cervical length measurement
14			BP[a] measurement			
16			BP measurement	OGTT[b] (in case of history of GDM[c])		Cervical length measurement and progesterone prophylaxis
18-20	Check-up (eg, BP and symphysio-fundal height measurements) and ultrasound screening for congenital abnormalities					Cervical length measurement
22			BP measurement			
24-26	Check-up		BP measurement	OGTT		Cervical length measurement
27	Additional blood tests (depending on Rhesus genotype)					
28			BP measurement and ultrasound fetal biometry	Ultrasound fetal biometry	Ultrasound fetal biometry	Cervical length measurement
30	anti-D immunoglobulin prophylaxis (depending on genotype)					
32	Check-up, blood tests (eg, hemoglobin), and ultrasound fetal biometry					Cervical length measurement
34			BP measurement			
36	Check up and ultrasound fetal biometry		Ultrasound fetal biometry		Ultrasound fetal biometry	
37			BP measurement			
38			BP measurement			
39			BP measurement			
40	Check-up and shared decision regarding induction of labor					
41-42	Check-up					

[a]BP: blood pressure.

[b]OGTT: oral glucose tolerance test according to the International Association of the Diabetes and Pregnancy Study Group's (IADPSG) criteria.

[c]GDM: gestational diabetes mellitus.

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Figure 1. Flowchart of participant enrolment and data collection of the Expect Study II. Whether or not a woman participates to the Expect Study II does not affect the health care women receive during their pregnancy.
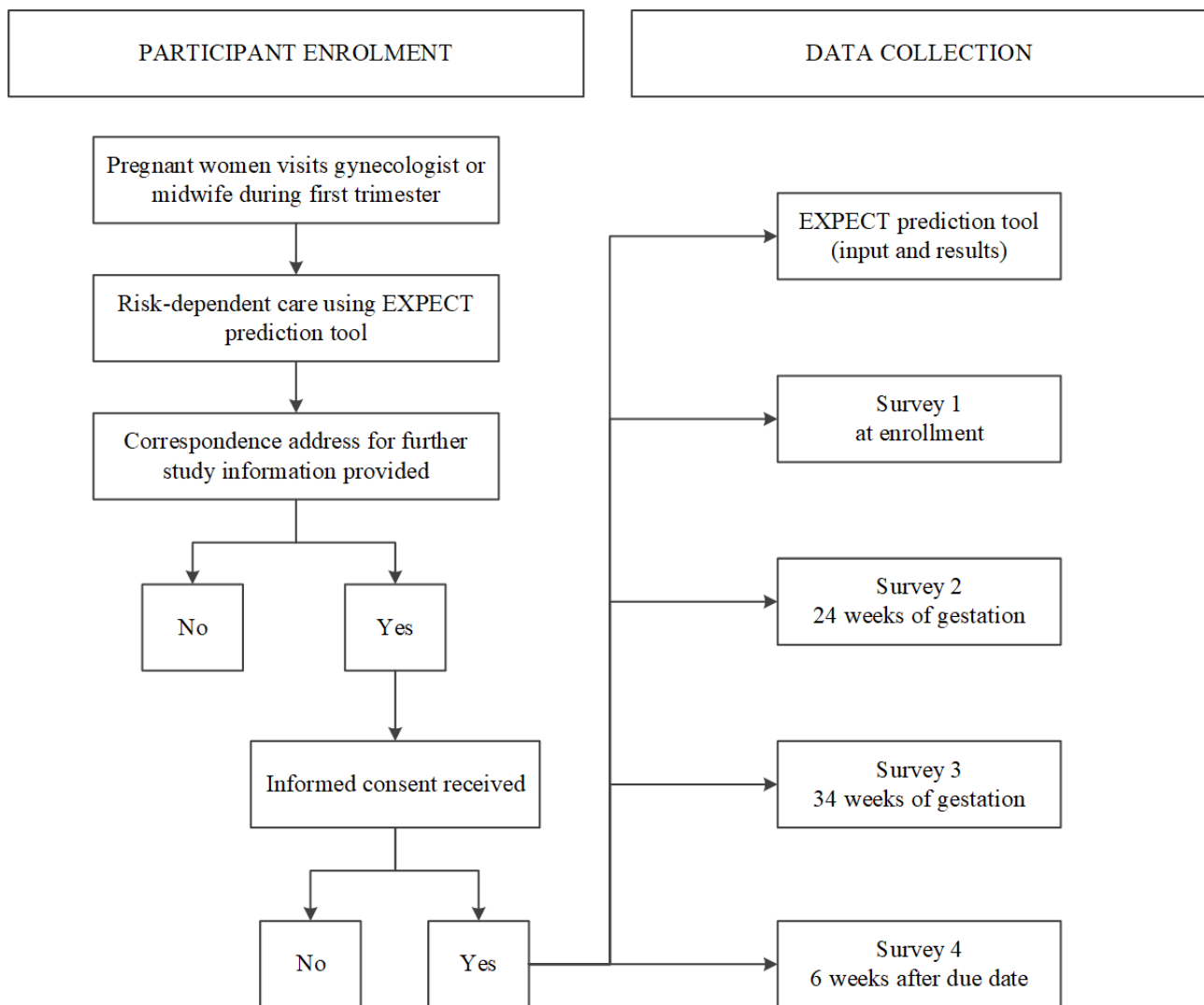
In order to document the nature and volume of health care resource used, women will be asked to record all visits to midwives, hospitals, and other care institutions. Furthermore, questions related to medication use, hospital admission, diagnostic and medical procedures, and the delivery will be asked. To minimize patient recall problems, information regarding the usage of health care resources will be requested at three intervals (surveys two, three and four) during the study period.

Survey four, the postpartum survey, addresses obstetric outcomes, compliance of health care recommendations, and the topics mentioned in survey two and three. Furthermore, this survey also contains questions regarding the health care consumption related to the neonate.

Sample size

According to the results of the validation study (Expect I) we expect approximately 30% of women to have an elevated estimated risk of PE, the obstetric complication with the lowest incidence (unpublished study submitted by Meertens et al, January 2018). Furthermore, an adherence of 70% and a compliance of approximately 40% is expected for the recommended aspirin treatment. This will result in approximately 21% and 12% respectively of the general population having an elevated risk of PE. In order to estimate these percentages with a precision of approximately 4% the required sample size is estimated at 400 participants [18].

Statistical Analysis

Missing values will be handled by imputation. Stochastic regression imputation with predictive mean matching as the imputation model will be used to prevent biased results based on complete case analysis only [19].

Adherence will be calculated by the proportion of women who reported to have received the LOC recommendations regarding adequate vitamin D and calcium intake, preventive aspirin treatment, and OGTT. Answers of participants will be linked to their estimated risk profile based on the Expect prediction tool.

Compliance will be analyzed by calculating the proportion of women who complied with the recommendations received from their health care professional regarding aspirin treatment, OGTT,

vitamin D, and calcium intake. Vitamin D is analyzed based on supplement intake and sunlight exposure. Calcium intake is determined by calculating the daily intake from diet and supplement use. Dietary intake will be estimated using answers from a selection of questions from the Dutch National Food Frequency Questionnaire tool [20]. These questions address food products that cumulatively cover >80% of the variance in calcium intake [21]. Total intake of both nutrients will be compared with the recommended intake by the LOC (1000 milligram calcium per day and 10 microgram of vitamin D per day) in order to determine compliance to these recommendations.

The secondary outcomes, patient satisfaction and cost-effectiveness, will be analyzed by comparing Expect Study II with the outcomes of former care-as-usual (Expect Study I). Patient satisfaction scores will be analyzed using multiple linear regression.

For the economic evaluation, we will use a health care perspective according to the Dutch guidelines for cost calculations [22]. A time horizon of approximately eleven months, from onset of pregnancy up to six weeks post-partum, will be applied. Maternal quality of life will be evaluated using the Euroqol EQ-5D-3L and EuroQol Visual Analogue Scale (EQ VAS) questions which are incorporated in the surveys. The EQ-5D-3L and EQ VAS are standardized questionnaires used worldwide to assess quality of life. Maternal QALYs will be calculated using the corresponding utility scores based on the Dutch population [23,24]. All costs will be expressed as 2017 Euros and if necessary cost prices will be transformed to 2017 Euros using the Dutch Consumer Price Index [25]. Bootstrap- and standard sensitivity analyses will be performed to quantify the uncertainty regarding the cost-effectiveness outcomes.

Results

Currently, women are being recruited for the Expect Study II and a total of 300 women are enrolled. We expect to achieve our goal of 400 participants during April 2018 and postpartum data collection will be finished by March 2019. As a result, first study results are expected in 2019.

Discussion

This paper describes the protocol of an impact study regarding the implementation of externally validated prediction models combined with risk-based care pathways in obstetric care. Prediction models are becoming increasingly popular in medicine [26]. Although the number of prediction models being published has increased tremendously in recent years, the number of external validation studies remains small [26]. Furthermore, performances of models predicting adverse pregnancy outcomes and the efficacy of preventive interventions for these outcomes are generally documented separately

[8,27,28]. Impact studies, describing the effect of using prediction models in daily practice combined with preventive interventions relevant to the estimated risk are nearly non-existent [26]. To the best of our knowledge no impact studies using prediction models in general obstetric practice have been published.

The strengths of our design are the multicenter prospective data collection and the similarity of both cohorts. Recruitment in multiple centers, hospitals and midwife clinics, improves the probability of collecting a representative sample of the obstetric population. This is essential in the Netherlands, since most pregnant women receive antenatal care by midwives at outpatient clinics [29]. Furthermore, optimal measurement of the outcomes is achieved by prospective data collection [30]. Finally, because the two cohorts are kept as similar as possible, we are able to accurately compare the former care-as-usual with the new risk-dependent care.

Some limitations of the design must also be noted. First, since the comparison of secondary outcomes of Expect II with those of Expect I is essentially a before-and-after comparison, time trends in the outcomes can theoretically influence results. In the interpretation of the results, we will take such trends into account, fro exmaple, by looking at trends in the studied outcomes from other regions in the Netherlands.

A second possible limitation of our study is that several outcomes will solely be based on participant questionnaires. Potential recall bias, however, is limited due to the prospective design and the usage of 4 questionnaires at limited intervals. Additionally, questionnaires have been shown to be a valid method of data collection regarding perinatal outcomes and medication exposure during pregnancy [31,32]. In the questionnaires we urge respondents to answer honestly and emphasize that all answers will be treated confidentially and will not influence the care provided by their obstetric health care professional. Furthermore, the additional procedures recommended in the risk-dependent care path are all subject to a shared decision-making process between woman and health care professional. As a result, we expect there is currently no taboo regarding the compliance with given recommendations.

We hypothesize that risk-dependent care results in early detection or prevention of obstetric adverse events and can thus reduce prevalence of neonatal adverse events. However, due to low prevalence rates of approximately 5%, large cohorts (approximately two times 6,800 participants) are necessary in order to achieve sufficient power to detect a reduction of at least 20% [18]. Therefore, the influence of risk-dependent care on the incidence of the neonatal composite outcome will be analyzed using registry data of the region. Moreover, to achieve the desired effects of risk-dependent care, it first needs to be implemented successfully. Thus, implementation should first lead to behavioral changes for both health care professionals and pregnant women.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report.

[PDF File (Adobe PDF File), 1MB - resprot_v7i5e10066_app1.pdf]

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Abbreviations

BP: blood pressure
EQ VAS: EuroQol Visual Analogue Scale
GDM: gestational diabetes mellitus
IADPSG: International Association of the Diabetes and Pregnancy Study Group
ICER: incremental cost-effectiveness ratio
LGA: large-for-gestational-age
LOC: Limburg Obstetric Consortium
OGTT: oral glucose tolerance tes
PCQ: Pregnancy and Childbirth Questionnaire
PE: pre-eclampsia
PTB: preterm birth
QALY: Quality Adjusted Life Year
SGA: small-for-gestational-age infancy

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Protocol

A Role for New Brain Magnetic Resonance Imaging Modalities in Daily Clinical Practice: Protocol of the Prediction of Cognitive Recovery After Stroke (PROCRAS) Study

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Abstract

Background: Cognitive impairment is common after acute ischemic stroke, affecting up to 75% of the patients. About half of the patients will show recovery, whereas the others will remain cognitively impaired or deteriorate. It is difficult to predict these different cognitive outcomes.

Objective: The objective of this study is to investigate whether diffusion tensor imaging–based measures of brain connectivity predict cognitive recovery after 1 year, in addition to patient characteristics and stroke severity. A specific premise of the Prediction of Cognitive Recovery After Stroke (PROCRAS) study is that it is conducted in a daily practice setting.

Methods: The PROCRAS study is a prospective, mono-center cohort study conducted in a large teaching hospital in the Netherlands. A total of 350 patients suffering from an ischemic stroke who screen positive for cognitive impairment on the Montreal Cognitive Assessment (MoCA<26) in the acute stage will undergo a 3Tesla-Magnetic Resonance Imaging (3T-MRI) with a diffusion-weighted sequence and a neuropsychological assessment. Patients will be classified as being unimpaired, as having a mild vascular cognitive disorder, or as having a major vascular cognitive disorder. One year after stroke, patients will undergo follow-up neuropsychological assessment. The primary endpoint is recovery of cognitive function 1 year after stroke in patients with a confirmed poststroke cognitive disorder. The secondary endpoint is deterioration of cognitive function in the first year after stroke.

Results: The study is already ongoing for 1.5 years, and thus far, 252 patients have provided written informed consent. Final results are expected in June 2019.

Conclusions: The PROCRAS study will show the additional predictive value of diffusion tensor imaging-based measures of brain connectivity for cognitive outcome at 1 year in patients with a poststroke cognitive disorder in a daily clinical practice setting.

Registered Report Identifier: RR1-10.2196/9431

KEYWORDS

stroke; brain infarction; cognitive dysfunction; diffusion magnetic resonance imaging; anisotropy; diffusion tensor imaging

Introduction

Stroke has a high global incidence of 41-316 per 100,000 persons per year [1]. Besides its physical consequences, cognitive deficits are common and occur in up to 75% of patients in the first weeks after stroke [2-5]. In half of the patients, cognition may improve [3,6]. Yet, long-term cognitive consequences of stroke include a twofold increased risk of dementia [7-9] and mild cognitive impairment [6]. Identification of those who will recover or who will have persistent cognitive impairment is important, as persistent cognitive dysfunction after stroke is independently correlated with worse long-term outcomes, such as independent living, community reintegration, and quality of life [10-14]. Moreover, recovery may be stimulated further in patients who are prone to improvement. For example, rehabilitation programs could use this information in setting realistic and attainable therapeutic goals.

Prediction of long-term cognitive outcome after ischemic stroke is, however, still inaccurate. Evidence is emerging on predictors of poor outcome, including demographic variables (eg, older age and lower level of education [2,3]). Brain imaging measures such as size and location of a stroke, the degree of white matter disease, and regional atrophy [15-21] may also determine cognitive function and long-term outcome after stroke. In contrast, fewer studies have addressed predictors of cognitive recovery among individuals with early poststroke impairment. Factors that have a positive effect on cognitive recovery are a stroke located in the right hemisphere and smoking [22,23], whereas neglect, depression, and apathy have a negative influence on cognitive recovery [23-25].

Measures of brain connectivity are of particular interest in this context. Stroke not only affects local connectivity but can also cause remote brain changes, as shown by functional MRI and diffusion tensor imaging (DTI) studies [26]. The value of brain connectivity measures has already been established for the prediction of motor recovery [27,28]. Conceivably, the relevance of measures of brain connectivity in vascular cognitive disorders (VCD) is also increasingly recognized. For example, global network efficiency assessed with DTI has been independently associated with cognitive performance in patients with cerebral small vessel disease [29-32]. Moreover, brain connectivity measures are correlated with cognition and intelligence in healthy controls [33,34] and have been suggested to provide an indication of brain resilience [34]. As such, it can be hypothesized that these measures could predict cognitive recovery after stroke. A recent study supporting this hypothesis showed that brain connectivity measures predict applied cognitive functioning 6 months after stroke [35]. Moreover, another study showed that an increased structural integrity of the contralesional hemisphere was associated with cognitive recovery after stroke [36].

The primary aim of the Prediction of Cognitive Recovery After Stroke (PROCRAS) study is to investigate whether DTI-based measures of brain connectivity predict cognitive recovery in the first year after stroke in patients with a confirmed poststroke cognitive disorder in addition to clinical, neuropsychological, and conventional imaging variables. Secondary aims are to assess the relation of DTI-based measures of brain connectivity with other outcomes. These other outcomes include deterioration of cognitive function, cognitive complaints, quality of life, participation, global health, and functional outcome. PROCRAS will also assess the feasibility of an extensive work-up including cognitive assessment and DTI in daily clinical practice.

Methods

Design

The PROCRAS study is a longitudinal, prospective, mono-center cohort study of cognition in patients with acute ischemic stroke, who will be followed for 1 year using 5 assessments.

Patient Population

Patients will be recruited from the stroke unit of the Elisabeth-Tweesteden Hospital Tilburg, the Netherlands. This is a hospital with an admission rate of approximately 700 patients per year for the diagnosis of acute ischemic stroke. Figure 1 visualizes the anticipated patient flow; the numbers are estimated and based on unpublished pilot data and a feasibility study performed in Heidelberg [37]. In all patients admitted with a clinical diagnosis of acute ischemic stroke, aged 50 years or older, the Montreal Cognitive Assessment (MoCA) [38] is administered as part of routine care. Patients with a score below 26 (screen positive) are eligible for inclusion (Textbox 1). MoCA assessment will be reattempted if at first patients are untestable. Exclusion criteria are prestroke dementia (known diagnosis of dementia or Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE≥3.6) [39]; life expectancy of less than 1 year; severe stroke expected to require long-term nursing care facilities, making patients not eligible for rehabilitation therapy; history of major neurological disease interfering with cognitive functioning; prestroke dependence in activities of daily living; insufficient command of the Dutch language; inability to participate in a neuropsychological assessment (eg, due to poor vision, severe aphasia, or if the patient is deemed untestable); and an impossibility to undergo an MRI of the brain (Textbox 2). If there is no information regarding the IQCODE, the researchers will discuss with the attending physician whether there are signs of pre-existing cognitive dysfunction. Only if there is no suspicion of prestroke dementia, patients are eligible for inclusion.

Additionally, 60 patients with a MoCA score of 26 or higher (screen negative) will be included as a reference group, matched for age and gender to the screen-positive patients (frequency matching). For this reference group, the other inclusion and exclusion criteria and study procedures are identical to the screen-positive patients.

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Figure 1. The expected patient flow in the Prediction of Cognitive Recovery After Stroke (PROCRAS) study. The target is to include 300 screen-positive patients at T2. Other numbers are estimated based on this target (MoCA: Montreal cognitive assessment; MRI: magnetic resonance imaging).
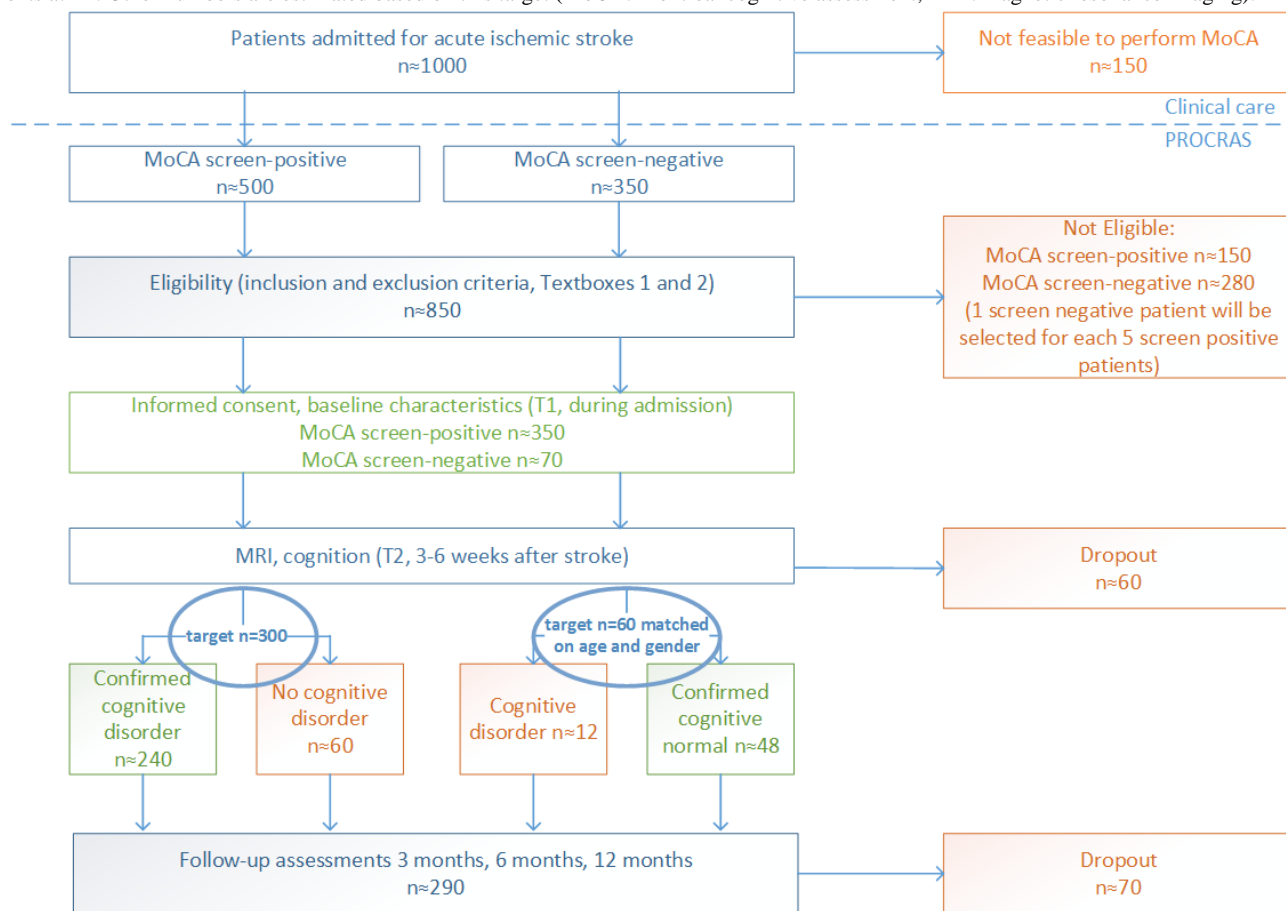
Textbox 1. Inclusion criteria.

- Clinical diagnosis of ischemic stroke

- Age ≥50 years

- Montreal Cognitive Assessment (MoCA) <26 (MoCA≥26 for the reference group)

Textbox 2. Exclusion criteria.

- Prestroke dementia: Known diagnosis of dementia or Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) ≥3.6

- Life expectancy <1 year

- Severe stroke expected to require long-term nursing care facilities

- History of major neurological disease interfering with cognitive functioning

- Prestroke dependence in activities of daily living (Barthel Index<18)

- Insufficient command of the Dutch language to participate and understand questionnaires

- Impossibility to participate in a neuropsychological assessment

- An absolute contraindication to undergo an magnetic resonance imaging MRI-scan of the brain

Figure 2. An overview of the procedures to be performed on each time point (IPAQ: the International Physical Activities Questionnaire; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; BI: Barthel Index; CIRS: Cumulative Illness Rating Scale; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; MRI: Magnetic Resonance Imaging; DTI: Diffusion Tensor Imaging; MoCA: Montreal cognitive assessment; HADS: Hospital Anxiety and Depression Scale; CLCE-24: CheckList for Cognitive and Emotional problems after stroke; SSQOL: Stroke Specific Quality of Life Scale; USER-P: Utrecht Scale for Evaluation of Rehabilitation-Participation; PROMIS: Patient-Reported Outcomes Measurement Information System; SEsx: Self-Efficacy for Symptom Management Scale, NPI-Q: Neuropsychiatric Inventory Questionnaire).

	Timing and setting	Demographics and prestroke condition	Neurological functioning and risk factors	Imaging	Cognitive status	Outcomes
T1	Acute stroke stage, during admission	Demographic factors Prestroke physical activities (IPAQ) Prestroke cognition (IQCODE) Prestroke activities of daily living (BI) Prestroke comorbidity (CIRS)	Stroke characteristics Stroke severity (NIHSS) Current ADL activities (BI) Functional status (mRS) Vascular risk factors Laboratory findings		Cognitive screening (MoCA)	
T2	3-6 weeks after stroke, outpatient clinic		Motor functioning (MI)	MRI + DTI	Neuropsychological assessment	Emotional functioning (HADS)
T3	3 months after stroke, telephonic interview		Functional status (mRS)			Cognitive complaints (CLCE-24) Quality of life (SSQOL) Participation (USER-P) Global health (PROMIS) Self-efficacy (SEsx)
T4	6 months after stroke, telephonic interview		Functional status (mRS)			
T5	1 year after stroke, outpatient clinic		Motor functioning (MI) Functional status (mRS)		Neuropsychological assessment	Cognitive complaints (CLCE-24) Quality of life (SSQOL) Participation (USER-P) Global health (PROMIS) Self-efficacy (SEsx) Emotional functioning (HADS, NPI-Q)

It is expected that the inclusion target will be reached in 1.5 years. Patients are treated the same way as patients that do not participate in this study. This study does not interfere with treatment choices or rehabilitation therapy. To account for any confounding, it will be registered whether patients received rehabilitation therapy and what kind of therapy was provided. Moreover, basic demographic data will be collected on the source population to understand what patient population participates in the PROCRAS.

Procedure

After informed consent, baseline characteristics will be assessed during hospital admission (T1). The second assessment takes places in an outpatient clinic 3-6 weeks after stroke (T2); the third assessment is a telephone interview 3 months after stroke (T3); the fourth assessment is another telephone interview 6 months after stroke (T4); and the fifth assessment is performed in an outpatient clinic 1 year after stroke (T5; see Figure 2). The PROCRAS study is ongoing for 18 months. From the first 100 patients at T2, 94 completed follow-up until T5.

Measures

Neuropsychological Assessment

The neuropsychological assessment will be performed at T2 and T5. It is designed using the "60-minute protocol" as proposed in the vascular cognitive impairment harmonization standards [6]. Textbox 3 lists the domains and associated tests. Presence or absence of poststroke cognitive impairment is operationalized according to the criteria for VCD [40]. Patients will be classified in 3 groups:

1. Unimpaired (performance on all domains is better than 1 SD below appropriate norms)
2. Mild VCD (performance on ≥1 domains is ≥1 SD but <2 SDs below appropriate norms)
3. Major VCD (performance on ≥1 domains is ≥2 SDs below appropriate norms).

The raw score for each test will be converted into a T-score corrected for age, gender, and level of education, when possible. The score for a domain is calculated by averaging the T-scores of the tests constituting that domain. The T-score is standard score with a mean of 50 and a SD of 10. For example, a T-score of 30 translates to 2 SDs below the mean, and a T-score of 60 corresponds to 1 SD above the mean.

Only for the bells test, no normative data are available. An abnormal score on this test will be defined based on a cutoff score of a difference of 5 or more omissions between columns 1-3 and columns 5-7 [41].

Magnetic Resonance Imaging

MRI data will be acquired on a Philips 3 Tesla scanner (Intera, Philips, Best, the Netherlands) for each patient at T2 using a standardized scanning protocol. The protocol consists of a sagittal 3D T1-weighted, an axial T2-weighted, an axial fluid attenuated inversion recovery, an axial diffusion-weighted imaging, and a DTI sequence. Brain tissue volumes and white matter hyperintensity volumes will be automatically determined by brain segmentation, and infarct volumes will be determined by manual segmentation [42,43].

Textbox 3. An overview of neuropsychological tests to be performed.

Attention and processing speed

- Reaction time test, Vienna Test System, S1, S2

- Symbol Digit Modalities Test

- Trailmaking test A

(Working) memory and learning

- Wechsler Adult Intelligence Scale (WAIS) Digit Span forward and backward

- The Rey Auditory Verbal Learning Test

Frontal-executive functions

- Controlled Oral Word Association Test

- Hayling test

- Reaction time test Vienna Test System S3

- Trailmaking test B

Language

- Boston naming test

- Semantic fluency

Visuospatial

- Bells test

Social cognition

- Facial Expressions Emotions Stimuli Test

DTI data will be analyzed and processed in ExploreDTI [44], as described earlier [45]. First, whole-brain fiber tracking will be performed. Second, the tract reconstructions are parcellated on 90 gray matter regions using the automated labeling atlas [46]. Third, a weighted connectivity matrix is obtained by scaling each present connection between each brain region by the mean fractional anisotropy of that connection. Finally, global network efficiency will be calculated by applying graph theory on the weighted connectivity matrix.

Other Parameters

At T1, demographic factors will be ascertained, apolipoprotein E (APOE) genotyping will be performed, stroke severity will be assessed using the National Institutes of Health Stroke Scale [47], comorbidity using the Cumulative Illness Rating Scale [48], pre-existent cognitive functioning using the IQCODE [39], pre-existent physical activities using the short form of the International Physical Activities Questionnaire [49], and pre-existent and current activities of daily living using the Barthel Index [50]. At T2 and T5, motor functioning will be assessed using the motricity index [51], and emotional functioning will be assessed using the Hospital Anxiety and Depression Scale [52] and the Neuropsychiatric Inventory Questionnaire [53].

At T3 and T5, self-efficacy will be assessed using the Self-Efficacy for Symptom Management Scale [54]; cognitive complaints using the Checklist for Cognitive and Emotional problems after stroke [55]; quality of life using the short version

of the Stroke Specific Quality of Life Scale [56]; participation using the Utrecht Scale for Evaluation of Rehabilitation-Participation [57,58]; and global health using the Patient-Reported Outcomes Measurement Information System [59,60]. Functional outcome will be assessed with the modified Rankin scale [61] at T1 and T3-T5.

Aims, Determinants, and Outcomes

Primary Aim

The primary aim of this study is to investigate whether DTI-based measures of brain connectivity predict cognitive recovery after 1 year, in addition to other determinants including patient characteristics and stroke severity. The main DTI marker that will be used is global network efficiency. This measure reflects the integration as well as the microstructural integrity of the white matter.

The primary outcome measure is recovery of cognitive function in the first year after stroke. This measure will be dichotomized into cognitive recovery and no cognitive recovery (ie, no change or deterioration). Cognitive recovery is operationalized as a transition from a mild VCD at 3-6 weeks (ie, T2) to no disorder at 1 year (ie, T5), or a transition from a major VCD at T2 to a mild or no VCD at T5. Hence, only patients with a confirmed VCD at T2 will be considered for this outcome. Patients that dropout will not be considered in the primary analyses. Their outcomes, obtained by telephone interview where possible, will be reported.

The secondary outcome measure is deterioration of cognitive function, operationalized as a transition from a mild VCD at T2 to a major VCD at T5 or a transition from no VCD at T2 to a mild or a major VCD at T5. For this outcome, only patients with no or a mild VCD at T2 will be considered.

In secondary analyses, we will also address change in cognitive performance as a continuous measure, using domain T-scores. For neuropsychological tests that require writing or drawing, we will take motor functioning into account as a covariate in the analysis.

Secondary Aims

A secondary aim is to assess the relation of DTI-based measures of brain connectivity with patient-reported outcomes and functional outcome. For this aim, the main DTI marker that will be used is, again, global network efficiency.

The outcome measures are cognitive complaints, quality of life, participation, global health, and functional outcome. The first 4 outcome measures will be assessed with questionnaires at 3 months after stroke (ie, T3) and 1 year after stroke (ie, T5). The questionnaires are repeated at T5 to assess whether a change in one of these measures occurs. Functional outcome is defined by the score on the modified Rankin Scale as assessed with a telephonic interview by a trained researcher at T1, T3, T4, and T5. All patients with completed follow-up until at least T3 will be considered for this analysis. Moreover, each of the outcome measures will be compared between the cognitive impaired group and the reference group.

Another secondary aim is to assess the feasibility of an extensive work-up including cognitive assessment and DTI in daily clinical practice.

The outcome measure will be the proportion of patients that underwent an MRI scan and neuropsychological assessment within the timeframe of 3-6 weeks at T2.

Figure 3 visualizes the primary and other outcomes of the PROCRAS study and the population used in the analyses.

Sample Size Calculation

On the basis of available literature, we estimate an area under the receiver operating characteristic (ROC) curve of 0.7 for the prediction model using clinical, neuropsychological, and conventional imaging parameters, and that approximately half of the patients with a confirmed cognitive disorder will recover [3,6,62]. When adding connectivity measures to this model, 200 participants are needed to detect an increase in the area under the ROC curve of 0.1 or more, with a power of 80% and an alpha of .05. As a rule of thumb, to reliably measure the weight of a predictor, at least 10 outcome events per predictor in a multivariate model are needed. This means that a maximum of 10 predictors can be used in these models. We estimate that 30% of the patients will not complete the full study procedures until T5, and that 80% of the screen-positive patients will have a confirmed cognitive disorder at T2. Therefore, we need to obtain around 300 screen-positive patients with data at T2, to obtain 200 patients with a confirmed cognitive disorder at T2 and complete follow-up until T5. We will include 1 screen-negative patient for every 5 included screen-positive patients in the reference group.

Figure 3. Outcomes of the Prediction of Cognitive Recovery After Stroke (PROCRAS) study and the population used in the primary analysis (VCD: vascular cognitive disorder; MoCA: Montreal Cognitive Assessment).
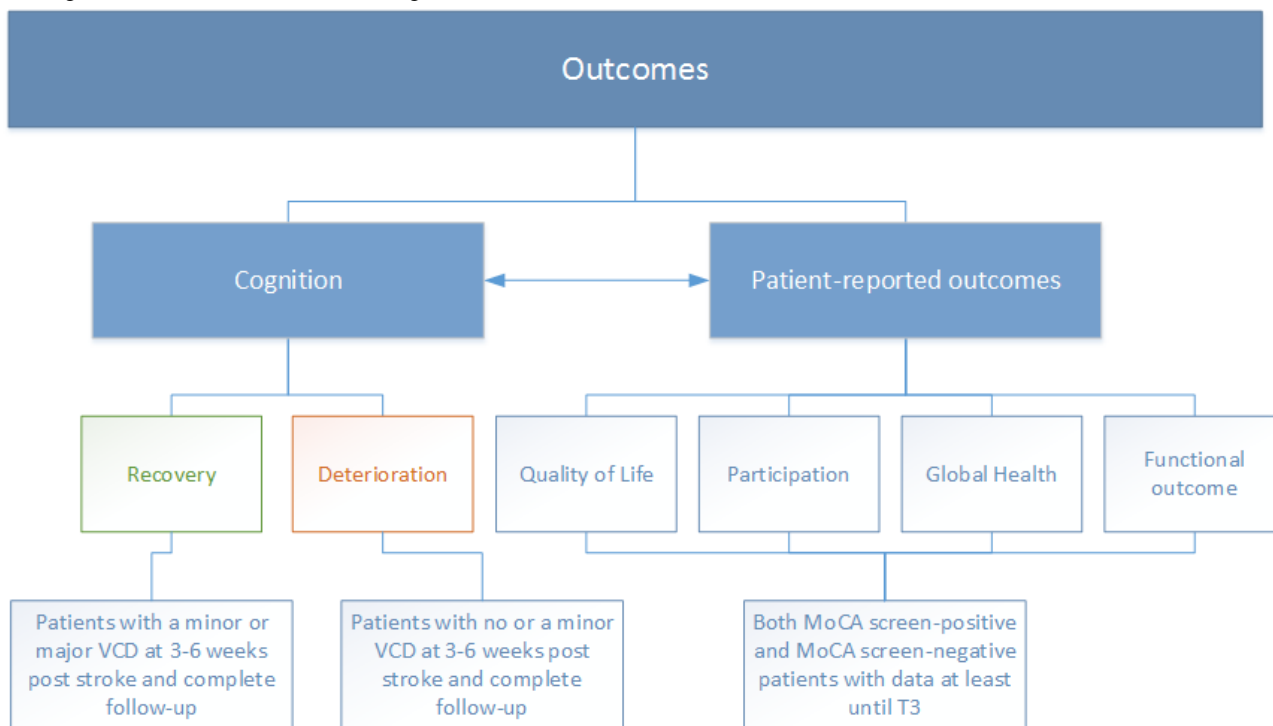
Statistics

First, descriptive statistics will be used. Second, to assess the additional value of DTI-based measures of brain connectivity, the 6 strongest predictors from clinical and conventional imaging parameters will be selected using univariable logistic regression with cognitive recovery as a dichotomous outcome measure. The predictive value of the multivariate model including the strongest predictors from clinical parameters and conventional imaging markers will be assessed. ROC analyses will be used to assess whether this predictive value can be improved by adding network metrics achieved from DTI. The same procedure will be performed in the prediction of the outcome measures related to the secondary aim. In the model, we will take the interval between the stroke and the assessment at T2 as covariate.

Regulation Statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

Ethics Committee Approval

The PROCRAS study was approved by the medical ethics committee of Brabant, based in Tilburg, the Netherlands. Written informed consent will be obtained from all participants.

Results

At time of acceptance of this paper for publication, this study has been ongoing for 20 months. Thus far, 252 patients have provided written informed consent. Final results are expected in June 2019.

Discussion

The PROCRAS study investigates whether DTI-based measures of brain connectivity predict cognitive recovery in a large stroke cohort in daily clinical practice in addition to known predictors of cognitive outcome. It adds to the existing literature because of several reasons.

First, it specifically focuses on cognitive recovery, using a selection of relevant determinants of cognitive outcome after stroke. As the mechanisms of cognitive recovery or deterioration after stroke are complex and involve multiple factors, a prediction model should incorporate each of the most important factors to provide reliable results. Moreover, by combining many of the known determinants in a large patient sample, the coherence between each of these factors can be better understood.

Second, this study combines the knowledge of different disciplines working in the stroke field, such as cognitive neuroscience, neuropsychology, and cognitive rehabilitation. Approaching VCDs from different angles may help us better understand how VCDs develop and how they continue to exist. Moreover, fundamental findings in cognitive neuroscience are not often translated in clinical practice [63]. If the diagnostic work-up proves to be feasible, results from this study can be implemented into clinical practice, benefitting individual stroke patients.

The study design has several limitations. First, the study focuses on a relatively specific patient group, because of several exclusion criteria. For example, patients that cannot undergo a neuropsychological examination due to severe aphasia are excluded. We have chosen to exclude patients with risk factors for a major VCI, as these patients have a low potential to show cognitive recovery. This would lower the sensitivity to find an effect. Second, this is a single-center study, which can affect generalizability of the results. Third, the timeframe of 3 weeks at T2 is rather broad. This might result in more patient variation, as patients show most recovery in the first weeks after stroke [64-66]. However, this timeframe of 3 weeks has been chosen for pragmatic reasons. At this point in time, information on the potential of cognitive recovery would help to make decisions in stroke rehabilitation.

In summary, the results of the PROCRAS study will support individualized PROCRAS. The results of this study may help in the psychoeducation of patients, they may add value to rehabilitation programs in setting realistic and attainable therapeutic goals, and they may help to anticipate the need for support.

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Authors' Contributions

PLMdK, JMS, JMAV, and GJB designed the study and obtained funding. HPA coordinates the study, manages the study and data collection, and wrote the first drafts of the manuscript. PLMdK, JMS, JMAV, and GJB provided comments on the first drafts of this manuscript. All authors read, commented on, and approved the final draft of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DTI: diffusion tensor imaging
IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly
MoCA: Montreal Cognitive Assessment
PROCRAS: Prediction of Cognitive Recovery After Stroke
VCD: vascular cognitive disorder

<u>Original Paper</u>

Translating Behavior Change Principles Into a Blended Exercise Intervention for Older Adults: Design Study

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Abstract

Background: Physical activity can prevent or delay age-related impairments and prolong the ability of older adults to live independently. Community-based programs typically offer classes where older adults can exercise only once a week under the guidance of an instructor. The health benefits of such programs vary. Exercise frequency and the duration of the program play a key role in realizing effectiveness. An auxiliary home-based exercise program can provide older adults the opportunity to exercise more regularly over a prolonged period of time in the convenience of their own homes. Furthermore, mobile electronic devices can be used to motivate and remotely guide older adults to exercise in a safe manner. Such a blended intervention, where technology is combined with personal guidance, needs to incorporate behavior change principles to ensure effectiveness.

Objective: The aim of this study was to identify theory-based components of a blended intervention that supports older adults to exercise at home.

Methods: The Medical Research Council framework was used to develop the blended intervention. Insights from focus group, expert panels, and literature were combined into leading design considerations.

Results: A client-server system had been developed that combined a tablet app with a database in the cloud and a Web-based dashboard that can be used by a personal coach to remotely monitor and guide older adults. The app contains several components that facilitate behavior change—an interactive module for goal setting, the ability to draw up a personal training schedule from a library containing over 50 exercise videos, progress monitoring, and possibilities to receive remote feedback and guidance of a personal coach.

Conclusions: An evidence-based blended intervention was designed to promote physical activity among older adults. The underlying design choices were underpinned by behavior change techniques that are rooted in self-regulation. Key components of the tablet-supported intervention were a tailored program that accommodates individual needs, demonstrations of functional exercises, monitoring, and remote feedback. The blended approach combines the convenience of a home-based exercise program for older adults with the strengths of mobile health and personal guidance.

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Introduction

Background

Physical activity (PA) is vital to a healthy life. A sedentary lifestyle is associated with numerous health-related problems such as obesity, diabetes, cardiovascular diseases, various forms of cancer, and depression [1,2]. Furthermore, for older adults, PA can prevent or delay the onset of functional impairments and prolong the ability to live independently [3]. Due to these well-acknowledged health benefits, community-based PA programs have spawned across the world [4,5].

A prototypical example of such a program that has been running for over 35 years in The Netherlands is "More Exercise for Seniors," abbreviated as MBvO in Dutch. Weekly, 300,000 older adults exercise in a group under the guidance of an instructor. A study evaluating the effects of this specific program, however, concluded that exercising once a week is not sufficient [6]. Studies show a higher frequency and a longer exercise duration is needed to capitalize on the health benefits of PA. At least 5 days a week 30 min of moderate-intensity PA is recommended [7,8], and additional weekly strength and balance exercises prevent the decline of muscle mass and flexibility of older adults [9,10].

This raises the question of how older adults can be stimulated to achieve the recommended levels of PA. First, convenience plays a role. Exercising in a community center several times a week is difficult to achieve due to the cost, time, and effort needed to travel [11]. To attain the recommended intensity, a home-based exercise program could prove a useful addition to a community-based program—in the convenience of their home, older adults can continue the exercises they have learnt during the weekly community classes.

Second, older adults need support in following an exercise program. In community classes, an instructor chooses which exercises are suited for the participants, provides instructions how they can be performed safely, and motivates the older adults to persevere. However, technology is increasingly being used for these functions. The potential to reach a large population and low costs are reasons for its emerging popularity. Various reviews indicate that technology-supported interventions can increase the effectiveness of exercise programs [12-17]. Most of the reported studies used websites to deliver the intervention. More recently, mobile health (mHealth), the use of mobile devices to deliver health solutions, however, has become popular [18]. In particular, for older adults, the use of tablets seems promising. Studies show that due to its large touchscreen, older adults are able to operate tablets better than personal computers [19,20] or smartphones [21]. The usability of tablets may be the reason for its increasing popularity in the United States [22] and The Netherlands [23,24] and its use in mHealth interventions for older adults [25].

Nevertheless, there are also limitations in the scope of mHealth. Automated feedback and guidance (ie, avatar coach) do not correspond well with the subtlety and social support that a person can provide [26]. A blended intervention, where personal guidance by a coach is matched with the possibilities technology can deliver, can be an effective approach. The blended intervention might be a useful extension of traditional community-based PA programs. It can increase the exercise frequency of such programs while relying on an existing infrastructure, such as the availability of instructors and the social support of peers.

Objective

As part of the VITAMIN (VITal Amsterdam elderly IN the city) and MOTO-B (MOtivating Technology for Older adults' Behavior) projects that aim to increase the vitality of older adults, we conceived a tablet-supported intervention to increase PA in older adults that currently participate in a community-based program by combining the convenience of a home-based program, the potential of mHealth, and the strengths of personal guidance. To develop an effective intervention, the following research question was addressed: How can theoretical principles and scientific evidence on behavior change be translated into features of a tablet-supported intervention to increase the PA levels of older adults?

The effectiveness of the intervention will be determined with a randomized control trial (RCT) that is currently ongoing. The procedure of the RCT is detailed in a protocol study [27]. In this study, we describe the design process that led to the blended intervention. The study meets the plea to transparently report how behavioral change interventions are developed [28]. In typical effect studies, either no theoretical underpinnings are provided or are loosely mentioned without giving a detailed report about how they have led to specific design and implementation choices. By sharing the process that led to the design, we attempt to contribute to this field.

Methods

The Medical Research Council Framework

To develop the blended exercise program, insights were drawn from scientific literature as well as from practice-based expertise. On the basis of the Medical Research Council (MRC) framework [29], the following steps were undertaken:

- Step 1: Identify attitudes of older adults
- Step 2: Identify scientific evidence and formulate design considerations
- Step 3: Identify requirements of the blended intervention
- Step 4: Design functional components
- Step 5: Implement components of the blended intervention.

After developing the intervention, the MRC framework recommends testing the intervention procedures and assessing the effectiveness in a controlled manner. These validation

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measures are discussed in the last section of the paper in light of follow-up studies.

Step 1: Identify Attitudes of Older Adults

Before developing the blended intervention, 8 focus groups were held with 48 older adults currently participating in the weekly MBvO community-based exercise classes. The aim was to explore the need for a blended intervention by investigating the attitudes of older adults toward an additional home-based exercise program and the possibility of supporting technology. The results show that participants recognized the benefits of doing home-based exercises. They had, however, also concerns regarding guidance, safety, and adherence to a home-based exercise program. The majority were open toward technology that could support them on those aspects, though some of them lacked the confidence to operate technical devices (see [30] for more details about the focus group study). Those insights fed into further development of the blended intervention.

Step 2: Identify Scientific Evidence and Formulate Design Considerations

To identify relevant literature, the ACM, IEEE, Google Scholar, PsycINFO, and PubMed databases were consulted. A combination of the following search terms was used—("older adults" OR seniors OR elder*), ("physical activity" OR exercise), (app OR internet OR web OR "mobile phone" OR smartphone OR tablet OR mHealth OR eHealth OR technology), and ("behavior change" OR adoption OR prevalence OR use OR attitude OR acceptance OR intent*). Forward and backward references were screened, and the recommender feature of Mendeley Reference Manager was used to identify additional sources. Studies that were assessed to be relevant, where precedence was given to reviews and meta-analysis, were selectively discussed with supervisors and peers from varying disciplines.

On the basis of the scientific evidence, 3 design considerations were formulated that address the issues identified in step 1.

Design Consideration 1: Functional Exercises

As people age, they lose muscle strength, flexibility, balance, and endurance. The decline across these 4 domains decreases their ability to perform activities of daily living (ADL); for instance, getting up from a chair, carrying groceries, or opening a jar [8]. A functional training program has shown to be more effective to counter this decline than general PA (ie, walking) or resistance training (ie, exercises with dumbbells) [31,32]. Functional training consists of exercises across the varying domains and is specifically designed to improve the performance of ADL. A functional exercise not only targets a daily task but also mimics its pattern. For instance, a functional exercise aiming to improve the mobility of older adults may contain exercises of walking up and down the stairs several times. Due to this close proximity to everyday life, older adults can integrate it autonomously into their daily routine. Furthermore, due to the resemblance, older adults recognize the relevance of the exercises more easily, which in turn improves the adherence to the training [33].

Design Consideration 2: Behavior Change

To regularly perform exercises at home, older adults have to develop new habits. The needed behavior change is hard to achieve, as indicated by the large part of the population that does not meet the recommended levels of PA and the low adherence rate to PA programs that seek to increase this [34,35]. Insights from the behavioral sciences can improve the effectiveness of these interventions. Notably, Michie et al [36] developed a taxonomy of 91 behavior change techniques (BCTs) that were synthesized from a wide body of evidence and afterwards refined to the CALO-RE taxonomy [37]. Techniques that are associated with the self-regulation of behavior appear particularly effective: goal-setting and self-monitoring [38]. In addition, techniques that increase self-efficacy, such as action planning and demonstrating behavior, are also shown to be effective [39]. When these techniques are combined with an evaluation phase in an iterative manner, it corresponds with the widely adopted control theory [40]. See Figure 1 for a schematic representation of the behavior change process adopted in this paper.

Figure 1. Behavior change through self-regulation.

Design Consideration 3: Blended Technology

Although the effectiveness of eHealth and mHealth to increase PA has been debated [41], 2 common success factors emerge from the literature.

First of all, feedback and guidance play a key role in enriching the various phases of the control theory. Several reviews underline the effectiveness of combining home-based exercise programs for older adults with (remote) guidance [39,41-44]. Geraedts et al [44] identified numerous studies that show higher adherence for home-based exercise intervention programs that included remote feedback. For instance, King et al [45] found the adherence rate of the home-based exercise program initially to be higher than the center-based program, but in a follow-up study [46], they reported a strong drop in adherence levels when the phone calls were ceased according to protocol after 1 year. Geraedts et al plead that PA interventions for older adults should utilize technology to support remote feedback and personal guidance.

The second success factor identified was tailoring. Krebs et al [14] concluded from a meta-analysis of various health behavior change studies, of which 25 targeted PA, that interventions with computer-tailored exercise programs were more effective than the control groups, with effect sizes varying from small to moderate. On average, 43% of participants in the eHealth groups adhered to the PA recommendations compared with 34% in the control groups. Furthermore, iterative tailoring was associated with a larger effect size than tailoring that was only done on the basis of baseline measurements, and this effect was stronger for longitudinal outcomes.

The importance of these 2 factors is also reflected by practice-based findings. The previously described focus group study (step 1) indicated that prospective participants believed additional home exercises would be a useful addition to the group-based classes, but also had worries about the motivation and adherence to such a program [30]. They value the personal guidance and feedback that the instructor provides during the weekly group-based classes. The majority of the participants were open to the idea of using supporting technology in doing exercises at home, though there were concerns if they were able to operate it.

Step 3: Identify Requirements of the Blended Intervention

By consulting experts from health sciences (requirement 1 and 3) and behavior science (requirement 2 and 4), leading requirements were formulated.

Requirement 1: Comprehensiveness

Following design consideration 1, the app should contain functional exercises that vary across domains and difficulty level that can be performed safely in a home setting. The exercises should target the strength, endurance, flexibility, and balance of older adults.

Requirement 2: Effectiveness

Following design consideration 2, the app should facilitate behavior change by supporting self-regulation.

Requirement 3: Adaptability

Following design consideration 3, the user should be able to create and customize a personal training schedule according to individual needs. Users should be able to increase or decrease the complexity as well as the physical load of the exercise.

Requirement 4: Remote Guidance

Following design consideration 3, the app should facilitate remote guidance by a personal coach to motivate and counsel users.

The identified requirements were discussed with practitioners who were involved with the community-based exercise programs for older adults. They confirmed the relevance of the requirements.

Results

After identifying the needs, design considerations, and requirements (step 1 to 3), consultation of behavioral scientist, computer scientist, and designers resulted in the design and implementation of the blended intervention (steps 4 and 5).

Step 4: Design Functional Components

By consulting a physical therapist and behavioral scientist, the 4 requirements that were formulated were translated into the components described below.

Comprehensiveness: Exercise Library

Users can browse through a library of 17 functional exercises. For each exercise, 3 variations are available that differ in complexity, amounting to a total of 51 exercise variations. Each exercise variation contains a video demonstration with a voice-over for verbal instructions, a factsheet with written instructions, and background information. The instructions stress how the exercises can be performed safely.

Effectiveness and Adaptability: Goal Setting

When using the app for the first time, older adults start out by filling in an interactive series of questions. First, they select the activities they value from a set of predefined ADLs. They then prioritize the selected ADLs by ranking these into a top 5 list. Finally, in the last step, the app recommends a number of exercises that match their goals. The user has the possibility to either add those exercises to their personalized exercise program or to ignore the suggestions. Moreover, users can commit to personal goals that they formulate themselves (free-choice alternatives).

Effectiveness and Adaptability: Action Planning

The exercise can subsequently be added to the personal training schedule of the user. When adding the exercises, users select the variation and the day they would like to perform the exercise. Optionally, they can set a reminder for a specific time to be alerted.

Effectiveness and Adaptability: Behavior Execution

Before performing the exercises as scheduled by the action planning app, users have the opportunity to watch a video in which an older adult demonstrates the exercise along with a

voice-over explaining various aspects. Furthermore, before execution, they can alter the physical load with 3 parameters—the duration of the exercise (30, 60, or 90 seconds), the number of repetitions (1, 2, or 3), and the intensity level (1, 2, or 3). During execution of the exercise, users are supported by a countdown timer that keeps track of the duration and repetitions.

Effectiveness and Adaptability: Self-Monitoring

After an exercise is performed, users are asked to rate the exercise with a visual analogue scale (slider) on 3 aspects: (1) the complexity of performing the exercise, (2) the effort it took, and (3) the likeability of the exercise. After rating the exercise, it is marked as completed. With checkmarks and progress bars, users can view their progress at a glance.

Remote Guidance: Videoconference

Users can make a video call to a personal coach. This coach has remote access to the personal schedule, the exercise parameters, and the ratings of the user. In dialogue with their personal coach, users can reflect on their progress by comparing their goals with their performance. If needed, they can adjust either their goals or the training schedule.

By employing creative brainstorming techniques (eg, scenarios, personas, wire-frames) during sessions with physical therapists, behavior scientists, and interaction designers, BCT defined by CALO-RE (Coventry, Aberdeen & London–Refined taxonomy) [37] were translated into envisioned functions of the tablet app. See Table 1 for the mapping.

Step 5: Implement Components of the Blended Intervention

Functional Exercises

The exercises were developed by a team of human movement scientists and physiotherapists. During the development of the program, active involvement of the older adults, PA trainers, and health professionals was arranged to guarantee that all exercises were understandable, feasible, and could be performed safely. Exercises were first piloted under supervised conditions in the group exercise setting, then under supervision at the older adults' homes, and finally by the older adults without direct supervision. During this process, the exercises and instructions were fine-tuned to achieve optimal functioning.

Envisioned Use Case During Randomized Controlled Trial

In line with the MRC framework, the blended intervention will be tested with an RCT. During this study, older adults are screened for eligibility, and a research coordinator assigns a personal coach to a user. The coach hands out the tablet to the user, along with a short written instruction on how to operate the device. Moreover, a short demonstration is given, and the user can try out the app himself. Then, the user starts by setting goals and drawing up a personal training schedule, assisted by the coach. After this, the user can perform the exercises independently at home. All activity on the tablet is sent to the server (goals, training schedule, and exercise ratings), which can be remotely monitored by the coach. At agreed times, the user seeks guidance of the personal coach by starting a video call within the app. User and coach reflect on the progress, and if needed, the user modifies his goals or training schedule afterward. This process can be done iteratively to support the self-regulation cycle. See Figure 2 for an overview of the use case.

Software Architecture

The functional components described in the previous step were implemented in a client-server system consisting of an app that was optimized for a 10-inch Android tablet, a back-end for data storage and communication, and a Web-based dashboard to establish communications with the human coaches. See Figure 3 for an overview.

On the tablet, users can set goals, view video demonstrations, create and modify personal training schedules, and rate exercises. The goals, training schedule, and exercises ratings of the user are securely sent to the back-end server and stored in a database. Personal coaches assigned to the users can login on a secured website and view the goals, training schedule, and exercise ratings of the user.

User Interface

To ensure the usability for older adults with no prior experience with mobile devices, simplicity was the guiding principle. Information was layered in various tabs, a metaphor based on an agenda or a Rolodex that older adults are familiar with was used. Furthermore, the visual design was also kept simple. The interface was kept clean with a limited number of elements. Exercises were represented by pictograms that could be viewed at a glance. Large font sizes and contrasting colors were used to ensure readability. To validate the interface, a small-scale usability test was done with 3 prospective users. Various minor modifications were made to improve the usability. See Figures 4-11 for an impression of the resulting user interface.

Table 1. Mapping between behavior change techniques and functions of the tablet app.

BCTs[a] as defined by CALO-RE[b]	Function of the tablet app
Identifying barriers or problem resolution	Videoconference with personal coach (intake)
Goal setting	Prioritize activities of daily living and formulating SMART (Specific, Measurable, Attainable, Realistic and Timely) goals
Setting graded tasks	Three variations of each exercise; before 3 execution parameters can be altered
Action planning	Tailored daily and weekly schedules
Prompt practice	Reminders or alarm
Instruction on how to perform the behavior	Voice-over instructions during video, written instructions in the specification sheet of each exercise, and countdown timer during exercises
Demonstrate behavior	Video depicting an older adult demonstrating how the exercise should be performed
Self-monitoring	Marking exercises as done; rating exercises on effort, complexity, and likeability
Provide feedback on performance	Videoconference with personal coach
Review of behavioral goals	Video conference with personal coach; modification of weekly schedule
Review of outcome goals	Video conference with personal coach; modification of SMART goals
Informing when and where to perform the behavior	Videoconference with personal coach
Environmental restructuring	Videoconference with personal coach
Training to use prompts	Videoconference with personal coach
Motivational interviewing	Videoconference with personal coach
Generalization of target behavior	Videoconference with personal coach
Facilitate social comparison	Weekly face-to-face classes
Plan social support	Weekly face-to-face classes

[a]BCT: behavior change techniques.

[b]CALO-RE: Coventry, Aberdeen & London–Refined taxonomy.

Figure 2. Overview of the use of the tablet app.
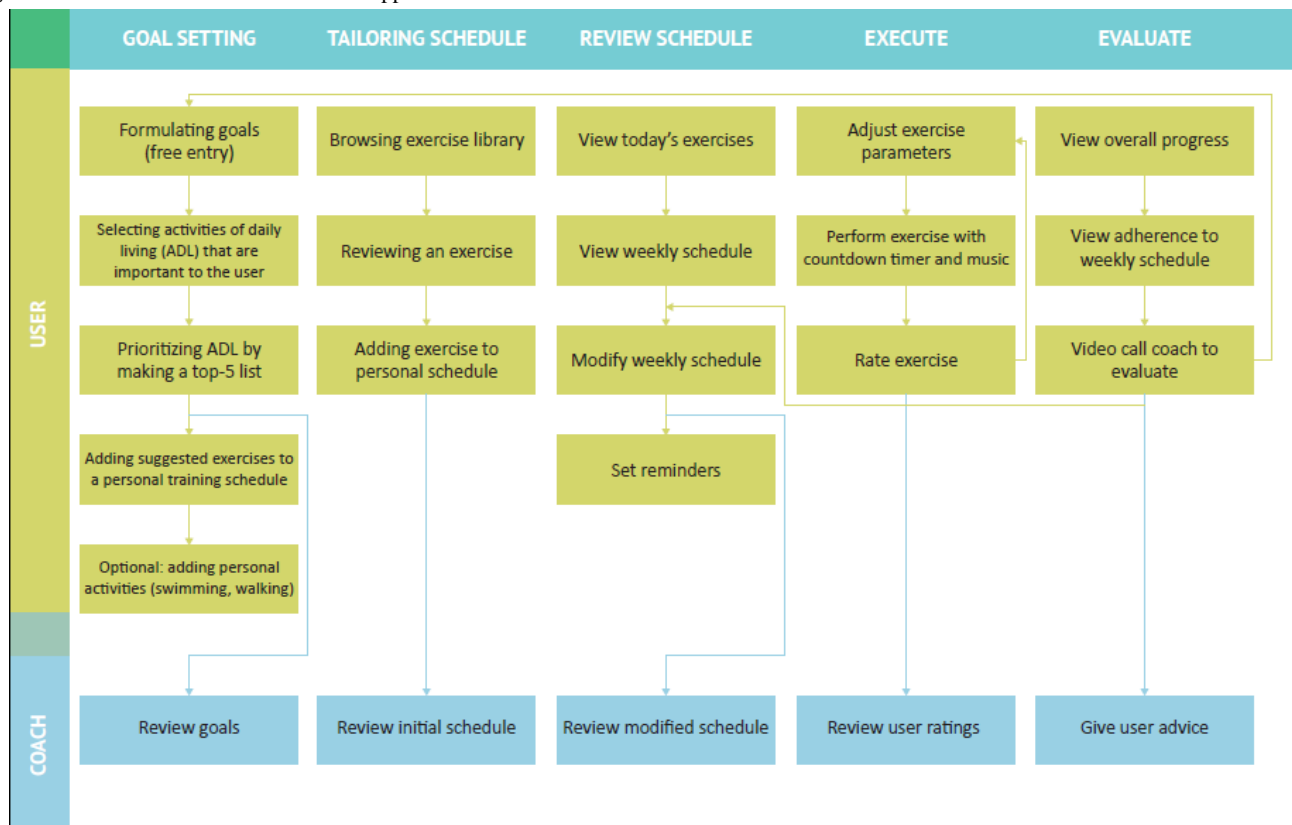
Figure 3. Information Technology architecture. MySQL: open-source relational database management system; APACHE: open-source web server; VITAMIN DB: database containing all relevant data; CMS: content management software; MBvO: More Exercise for Seniors; Android: operating system for tablet computers; Ubuntu: operating system for the server; HTTP/TLS: encrypted network traffic.
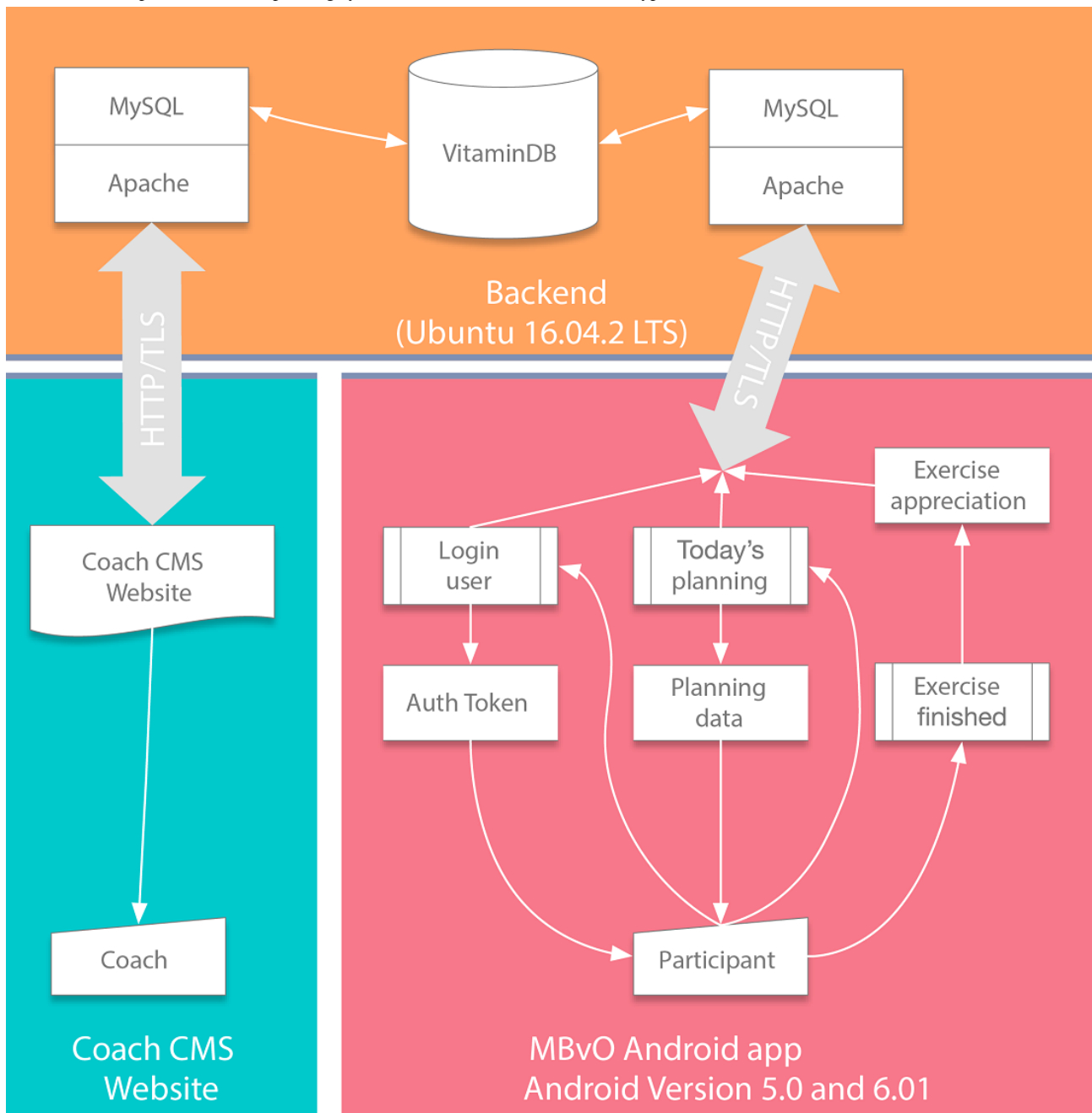
Figure 4. Exercise library.

Figure 5. Selecting exercise variation.

Figure 6. Personal training schedule.
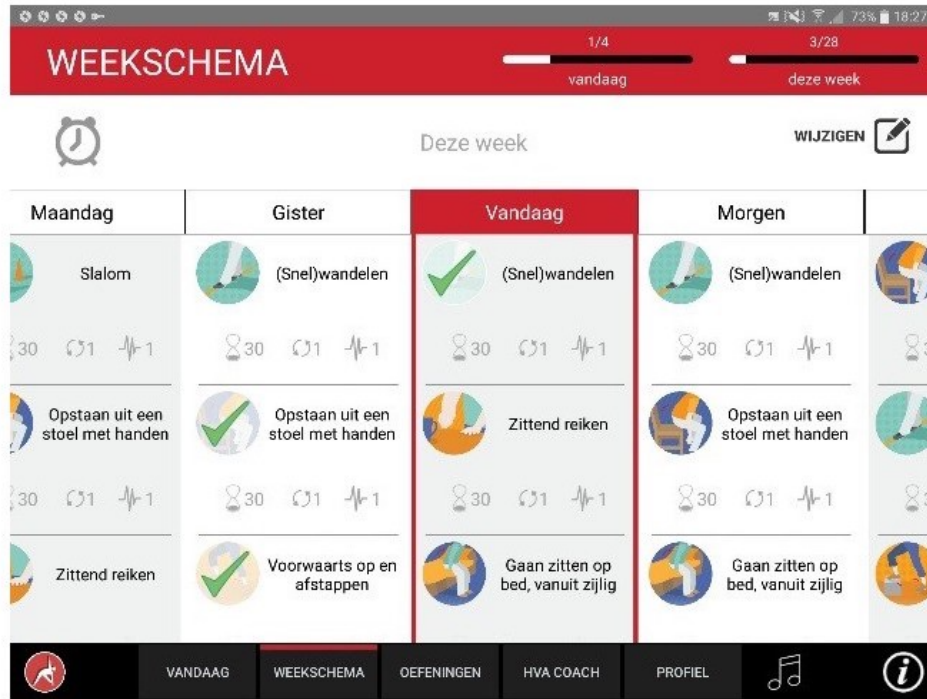
Figure 7. Today's program.

Figure 8. Modifying execution parameters.
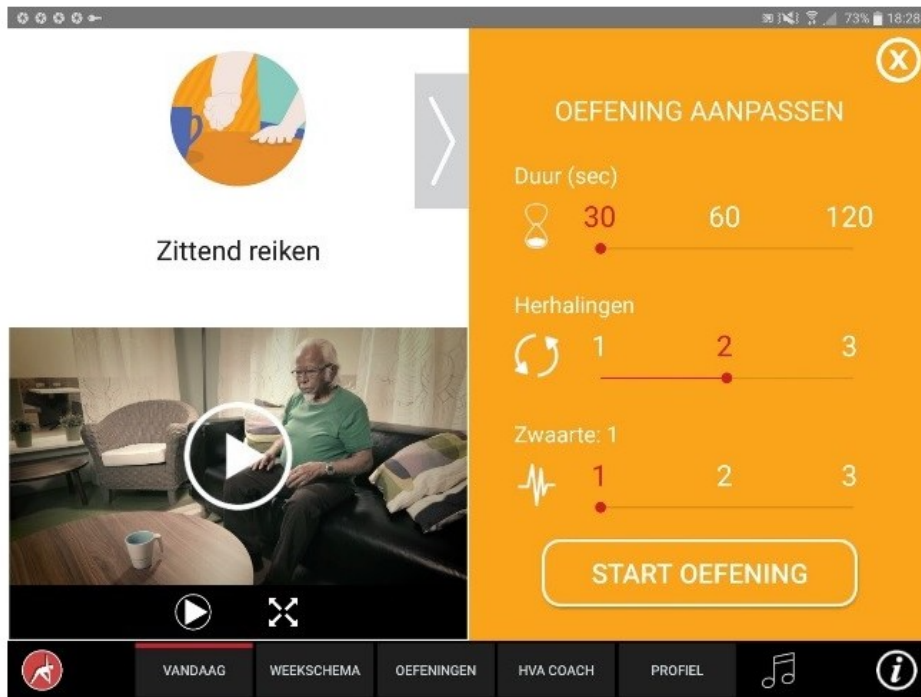
Figure 9. Countdown timer during executing.

Figure 10. Rating an exercise.
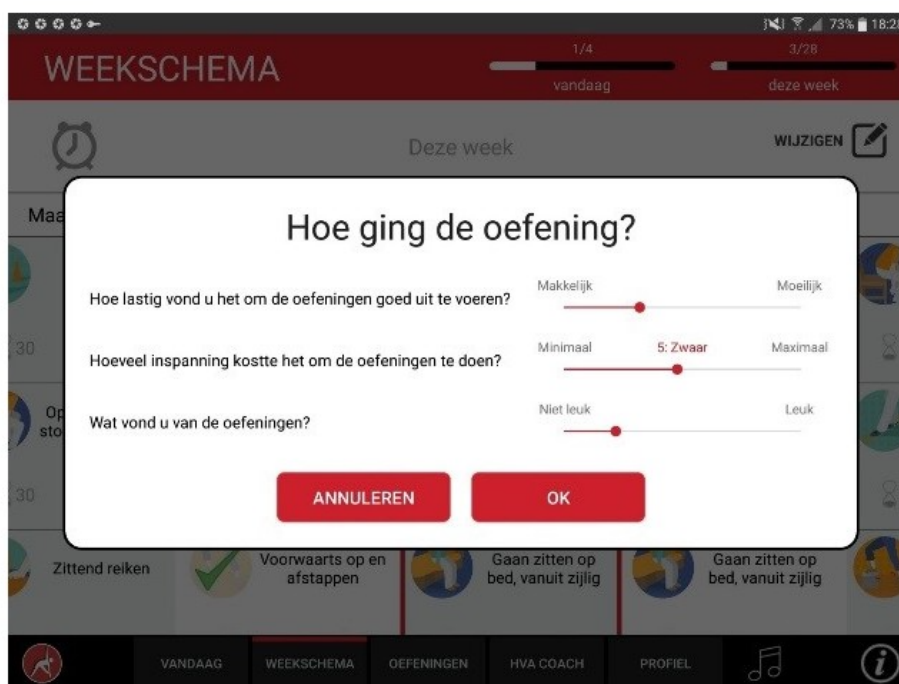
Figure 11. Initiating video call to coach.
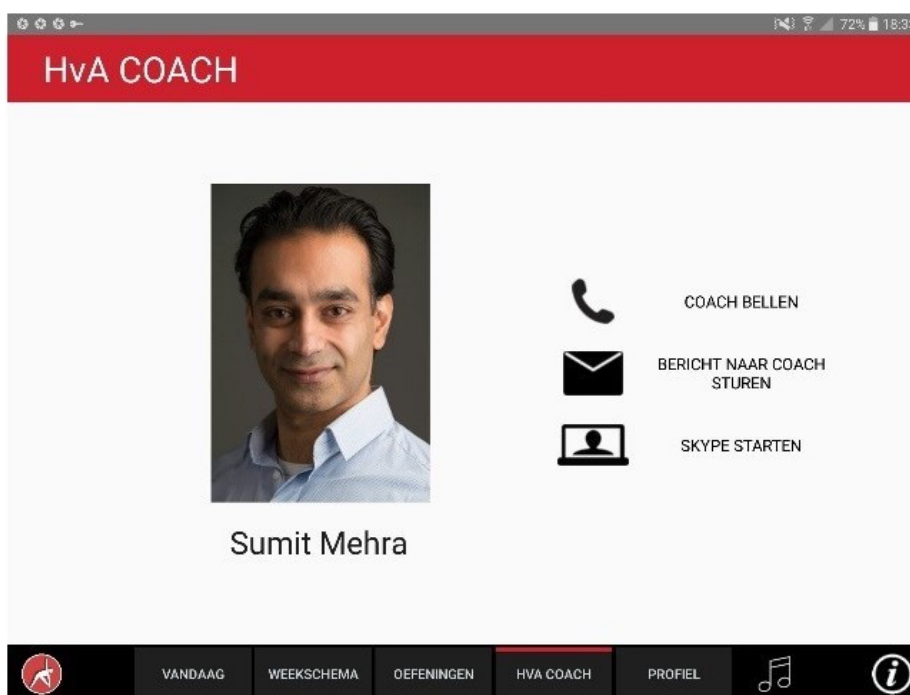
Discussion

Principal Findings

By following the MRC framework, a novel intervention has been developed to perform functional exercises at home. It is designed for older adults currently participating in weekly community classes to increase the frequency, duration, and intensity of exercises in a safe and convenient manner in a familiar setting. With a tablet, a customized training schedule can be compiled that matches the personal goals of the user.

Furthermore, for motivation and advice, the tablet facilitates remote guidance by a personal coach. Moreover, older adults not participating in community exercise programs can use the tablet autonomously, albeit without the auxiliary guidance of a personal coach. All the components of the blended intervention have been carefully selected and are based on the behavior change theory.

Contribution and Related Work

There is a wide body of evidence that health interventions that support self-regulation in the general adult population are

effective. For older adults, however, there are mixed results. French et al [47] found, in a systematic review, that interventions containing goal-setting and self-monitoring were remarkably associated with lower levels of PA in older adults. They suggest this may be caused by a decline in executive functioning associated with aging. Self-regulation requires cognitive effort. In the systematic review of Devereux-Fitzgerald et al [48], however, it is argued that supporting self-regulation is also important for interventions targeting older adults, but specific characteristics of this population have to be taken into account. Older adults value maintaining social relations with others and rather focus on short-term health benefits instead of long-term benefits. The blended intervention reported here takes those aspects into account by extending community-based PA programs, where social relations already exist [30]. Furthermore, the intervention facilitates personal guidance of a coach. Finally, the goals revolve around activities of daily living that are recognizable for older adults, instead of general (long-term) health benefits. Examples are joining their spouse for gardening or being able to go for a walk with their grandchildren. Furthermore, one could argue that providing tools such as a tablet help older adults overcome their declining ability to self-regulate behavior. Daily and weekly schedules and reminders, for instance, lower the cognitive effort needed for action planning.

The reviews mentioned earlier [47,48] describe general PA interventions for older adults. Only a few review studies specifically focus on the role technology can play to promote PA in older adults [25,41,49]. eHealth interventions that explicitly take social aspects into account are rare. Notable early work of Silveira et al [50] describes a pioneering study in which a tablet not only supported self-regulation but also social support. Older adults could, for instance, monitor progress of other participants and could send each other motivational messages. Nevertheless, the study failed to demonstrate a beneficial effect of facilitating social support. The question remains, however, if merely facilitating online communication between peers who are not acquainted with each other is sufficient to capture the richness of social interactions. In contrast to the work of Silveira, the blended intervention described in this study is designed to extend existing community-based programs that rely on weekly face-to-face classes. Therefore, the proposed intervention can rely on social relations that are already in place.

As noted by Khaghani-Far et al [26], the present computer-generated support, mostly in the form of a virtual coach, is not capable of replacing the emotional support provided by a human coach. The contribution of our work is the demonstration of how PA in older adults can be stimulated by a blended approach. To our knowledge, only 1 prior study had combined the benefits of a face-to-face exercise program to the possibilities of mHealth. Lee et al [51] provided older adults with a tablet which they used for doing home-based exercises 3 times a week during a period of 8 weeks, in conjunction with weekly group-based exercises. Although participants showed an increase in motivation, no difference in physical functioning was observed. As suggested by the authors, a reason for this absence might be the limited number of

participants in the trial (N=26) and the short duration of the study.

Limitations

The ability for older adults to draw up a personal training schedule is a key element of the design. Users can choose from a library containing approximately 50 different functional exercises. Furthermore, the duration, number of repetitions, and the intensity level of each exercise can be manipulated, amounting to roughly 500 unique exercise variations. Despite the ability to personalize the exercise program in great detail, there are still limitations to the tailoring. Older adults with specific limitations will not be able to perform some exercises in the manner demonstrated in the app or they may prefer outdoor activities above the home-based functional exercises (ie, taking a walk, riding a bike, gardening, etc). The variation in individual preferences is virtually unlimited. To accommodate this, the app was designed with the ability to add user-defined activities to the personal training schedule. The app allows the user to plan, monitor, and evaluate those exercises but does not contain instructions or video demonstration. The support for user-defined exercises is therefore somewhat limited.

Another key element of the design is the ability to receive remote feedback from a coach. As pointed out, the support by a human is more rich and effective than computer-generated feedback. There is, however, also a drawback. To be effective, feedback needs to be timely. Automated feedback can be near instant. In contrast, depending on the availability of the coach, older adults will have to wait some time to receive personal feedback.

A final limitation is the need for validation. The work presented here is ongoing. In line with the MRC framework, the developed intervention has to be validated rigorously by feasibility and effectiveness studies. First, older adults were involved during the development of the intervention—initially by conducting focus groups to explore their attitudes toward a blended intervention and afterwards to pilot the exercises and tablet use. Due to practicalities, however, the exercises and tablet use were evaluated separately. Older adults that participated in the evaluation of the tablet focused on the usability of the app; they did not actually perform the exercises. In contrast, the older adults that evaluated the exercises did so without the support of a tablet. Thus, how users perform exercises at home supported with a tablet still needs to be addressed with a more extensive usability study.

Second, the effectiveness of the theoretically underpinned intervention has yet to be empirically determined. During the next phase of the study, an RCT will cast light on to which extent the intervention leads to increased adherence and health benefits in the long run. This will extend the findings of Lee et al [51] by testing the blended intervention among a sufficiently large number of older adults (N=240) for a 12-month period. In addition, the RCT will investigate how the effects of the exercise program can be reinforced by dietary intake [27].

Conclusions

In summary, an evidence-based blended intervention was designed to promote PA amongst older adults. The underlying

design choices are underpinned by behavior change techniques that are rooted in self-regulation. Key components of the tablet-supported intervention are a tailored program that accommodates individual needs, demonstrations of functional exercises, (self-)monitoring, and remote feedback. The blended approach combines the convenience of a home-based exercise program for older adults with the strengths of mHealth and personal guidance.

Acknowledgments

Conflicts of Interest

None declared.

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Abbreviations

ADL: activities of daily living
BCT: behavior change technique
CALO-RE: Coventry, Aberdeen & London–Refined taxonomy
mHealth: mobile health
MRC: Medical Research Council
PA: physical activity
RCT: randomized controlled trial

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<u>Original Paper</u>

One Step Forward: Development of a Program Promoting Active School Transportation

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Abstract

Background: Physical activity promotes health and learning. However, up to 80% of the children in industrialized countries do not achieve the recommended level of daily physical activity. By encouraging children to use active school transportation (AST), it is possible to increase their overall physical activity.

Objective: The aim of this paper was to present the development of an AST intervention using Intervention Mapping (IM) to promote children's physical activity.

Methods: The principles of IM were applied to guide the development of the intervention. The process was divided into 3 phases. First, a literature review and collection of experiences of stakeholders were carried out to gain a broad perspective on the problem and possible solutions. Thereafter, an analysis of the critical environmental and behavioral factors affecting outcome was conducted, which guided the choice of tangible components of the intervention. Finally, a plan of evaluation and implementation was established.

Results: A structured program to increase AST among children was developed, consisting of 3 subsequent phases that are described in detail. Implementation took place, and evaluation of the intervention is being carried out.

Conclusions: IM proved to be a valuable method to develop a structured AST intervention for children. By following the steps of the IM process, it became evident that empowerment and gamification are 2 promising avenues to consider when designing AST interventions in a school context. By engaging end users and including important agents, such as parents and teachers, who control the environmental factors, the possibility to design a sustainable program increases. In addition, gamification made it possible to integrate learning into AST, which could motivate schools to devote time and effort to implementing this program.

Introduction

Background

Although many studies have illuminated the ways in which physical activity provides children with fundamental health benefits, children are not physically active to the extent that is needed [1]. Among Swedish children aged 11 years, only 21% of males and 13% of females achieve the recommended daily levels of physical activity [2]. This is even more problematic when considering the increasing problem with childhood obesity, which has risen substantially in most high-income countries over the last three decades [3]. To reach the recommended levels of activity, children could be encouraged to walk or bike to school, which are known as forms of active school transportation (AST) [4]. However, many industrial countries have seen a decline in AST among children and adolescents, and an additional decline is likely in the absence

of interventions to increase AST [5,6]. Though many studies have focused on the social and environmental factors that influence children's AST, the interventions developed have proven insufficient for promoting AST [7]. Only a few schools implemented these interventions, perhaps as a result of the disconnect between research and schools' needs [8]. To date, several concerns about school interventions for promoting physical activity have been highlighted in reviews. It has been pointed out that research has failed to determine the contextually sensitive attributes that define successful school-based interventions [9], and rigid scientific methodologies and evaluation techniques are incompatible with societally complex issues [10]. Given the disconnect between what was intended and how AST is carried out, there is a need to analyze physical activity interventions in schools to find ways to increase their feasibility and sustainability.

This paper aims to elucidate the logic model for the problem and the solution, as well as the theoretical underpinnings of an intervention promoting AST. Intervention research is defined as the process of creating the elements of an intervention and refining those elements through a series of studies [11]. By using theory and evidence as foundations in intervention research and by presenting multiple theoretical and experiential perspectives to solve a problem [12], other research teams can be inspired to build on this or prevent future mistakes. Intervention Mapping (IM) is both a framework and a structured way of planning, implementing, and evaluating health promotion programs [13]. The theoretical underpinning of IM is the social ecological model, which states that health is a function of the individuals living in an environment. Solving a health promotion problem requires a systematic perspective. The environments include physical, social, and cultural factors, in addition to agents exercising control over these factors at each ecological level, such as interpersonal, organizational, community, or societal environments.

Objective

The aim of this paper was to present the development of an AST intervention using IM to promote children's physical activity.

Methods

Intervention Mapping Tool

IM, a 6-step tool that maps the path from recognizing a problem to identifying a solution, was used to develop the program. The process was iterative rather than linear and the planners moved back and forth, as they gained new information and perspectives. The 6 steps include (1) logic model for the problem, (2) logic model for the solution, (3) program design, (4) program production, (5) program implementation plan, and (6) evaluation plan [13]. During program planning and execution, all planning group meetings were documented, as were field notes from every step of the process.

Participants

Program development was driven by a planning group consisting of the 2 authors with research experience concerning children and physical activity, one researcher with research experience concerning AST with a special focus on environmental

engineering, 2 teachers, the principal, and the head of the municipality's planning department.

The research project was performed in a municipality of approximately 80,000 inhabitants situated in northern Sweden. Five schools with infrastructure that could allow first-grade children to walk or bike to school were invited to participate in the study, and one school agreed to participate. This primary school had 270 schoolchildren, and the neighborhood included both apartment houses and detached houses. The 2 cohorts consisted of 45 children aged 7 to 8 years (25 males). The parents and the children were informed about the study by the authors, both face-to-face and in writing, and 42 children (23 males and 19 females) agreed to participate. All parents were also invited to participate, and 63 parents (26 fathers and 37 mothers) did so. Of the 63 parents, 46 had a college/university education and the remaining 17 had an upper secondary education. All but 2 were Swedish citizens. The distance between home and school varied between 0.2 and 6.0 km, with an average distance of 1.3 km.

Procedure

Program development began by forming the planning group, which was active during the whole project.

Phase 1

First, a logic model for the problem was formulated, which contained an assessment of the determinants and behavioral and environmental factors. On the basis of this model, a logic model for the solution was created. Gradually, these steps became increasingly intertwined. The phase was informed by a review of the theory and literature concerning children's physical activity interventions (in particular AST, empowerment, and gamification). In addition, several other contacts were made within the municipality, surrounding community, and related scientific areas of research in order to understand the community, its members, and the theoretical models for the problem and the solution. We created a joint logic model for the problem and for the solution, which were inspired by the 2 models of Bartholomew Eldredge [13].

Phase 2

Once the theoretical framework was established, it was used to guide the tangible program components. To be true to an empowerment approach, the program development was a partnership between the teachers, parents, and children that created something that they perceived to be meaningful.

Phase 3

This phase included a plan for evaluation and implementation. Preliminary results were presented and discussed during this phase.

Ethical Considerations

The study was performed in accordance with the principles of the Swedish law for research ethics and the Declaration of Helsinki's Ethical Principles for Medical Research Involving Human Subjects [14]. The study was approved by the Regional Ethical Board in Umeå, Sweden, before the start of the research

project (issue date: February 9, 2016; application registration number: 2015/296-31Ö).

Results

The outcomes of the IM process are described in 3 different phases. The process began with the formulation of a logic model for the problem and the solution, and it continued with the program design and production. Ultimately, an evaluation plan was established.

Phase 1: Logic Model for the Problem and Logic Model for the Solution

Theory- and Evidence-Based Factors Affecting Active School Transportation Behavior

To identify the factors related to AST behavior, social cognitive theory was used because it has been proven useful for developing effective physical activity behavior change interventions in children [15]. Social cognitive theory conceives of individuals within a collective context, as people do not operate as isolated individuals [16]. Social cognitive theory specifies a set of constructs, including knowledge, perceived self-efficacy, outcome expectations, goals, perceived facilitators, and impediments to change. Self-efficacy is altered by direct mastery experience, vicarious experience, and social persuasion [16]. Thus, self-efficacy might be applicable to this program because it could affect AST performance, modeling, and social support. Previous studies confirmed that self-efficacy mediates the causal pathway between interventions and children's physical activity levels [17]. However, research examining social cognitive theories and physical activity has largely focused on adult populations, and there is limited knowledge regarding children [12].

Research has recognized that gamification has great potential to promote children's physical activity and learning [18,19]. Gamification is defined as the use of game design elements in a nongame context [20]. The use of gamification enhances the possibility of capturing the components that make games engaging, and it can be used to improve the effectiveness of health promotion initiatives [21]. Promising research suggests that gamification can promote AST [22]. By using elements such as recurrent assignments that grant badges to students and allow them to level up to the next challenge, this approach can potentially ignite internal motivation to engage in healthy behavior. Acquiring badges can drive knowledge acquisition and behavior change [23].

The participatory elements of empowerment can improve an intervention's compatibility, and they increase the likelihood that effective programs will be sustained [24]. One study has shown that problems with intervention design and evaluation can be overcome by taking advantage of the end users' involvement and by explaining the connections among programs, policies, and evaluations [25]. We have previously performed promising school-based research using empowerment in order to promote physical activity [15]. According to Tengland [26], using an empowerment approach involves minimizing the influence of professionals, and the individual or group that is in need of support should take responsibility for the change process. Furthermore, empowerment and children's active participation can increase knowledge acquisition and competencies [27]. Yet, critics have claimed that professionals should not reduce their power over projects because professionals are part of the project and must have a say in decisions [26].

Agents Who Control Environmental Factors

In the social ecological model, parents are an important interpersonal factor. Because children in this program were only 7 to 8 years of age, their parents are the gatekeepers of their children's AST. Our previous research concluded that parents are important as role models, providing encouragement and tangible support [15]. Therefore, parental attitudes toward AST are a factor that could constitute either a problem or a means of facilitation. Using parental attitudes as a starting point and including them in program development are consistent with Bandura's theories [16] because environmental factors (such as social support) are a central element of both social cognitive theory and previous research [28]. However, few interventions have been based on parents' psychological factors on an intrapersonal level, such as parents' perceived barriers, outcome expectations, and self-efficacy [29].

An organization-level factor that is causally related to successfully increasing AST is school involvement. Promoting health might appear to be an added burden when the primary focus of schools is to meet academic standards. In fact, physical activity is sometimes seen as a competitor to academic studies because the time devoted to physical activity could instead be devoted to academic work [30]. Good health is critical for achieving an optimal education, and studies have found associations between children's physical activity and academic performance [31]. Moreover, research has shown that physical activity improves children's cognition and brain health [32]. This association should be a motivator for schools to be involved in increasing AST.

In this study, teachers were highly involved in the development of the program. For instance, they created special weekly assignments, were responsible for measuring distances for each child's AST, and helped determine how to use these data in their teaching. Therefore, engaging teachers is required for the success of an AST program.

Phase 2: Program Design and Production

Once the theoretical framework was established, the planning group addressed the critical environmental and behavioral factors that were most likely to affect the outcome (Textbox 1).

Textbox 1. Critical environmental and behavioral factors and actions that promote active school transportation (AST).

- Empowerment of school personnel

    - Action: Planning workshops, assignments, and measurement of AST

- Knowledge and motivation of parents

    - Action: Parenting meeting: discussion, assess attitudes toward AST

- Knowledge of children

    - Action: Workshops on health, environment, and safety

- Empowerment of parents and children

    - Action: Bring the ideas of parents and children into the AST program

- Motivation of children

    - Action: Gamification of AST measurement and weekly assignments incorporated into teaching

Environmental factors we identified were parental knowledge of AST, attitudes toward AST, and perceived AST barriers. Therefore, during a parenting meeting, we informed parents about the benefits of physical activity for their children in terms of both health and academic performance. We also let parents discuss their doubts and fears around letting their children walk and bicycle to school and discussed solutions. In addition, we assessed parental psychological factors on an intrapersonal level using a questionnaire and discussions during this meeting. We analyzed the results from the questionnaire, determined their specific worries, and suggested solutions that were used as a starting point for program design. The questionnaire was the Modified Integrated model for Children's Active Commuting to School, which has been shown to fit well with this model, and thus, may enable health behavior researchers to design effective interventions to promote AST [29]. Parents highlighted 2 main concerns: (1) having an accident when crossing roads with heavy traffic and (2) meeting a harmful person (stranger danger) while in transit during AST. Examples of suggested solutions used in the program were pairing children according to geographic location and encouraging them to walk or bicycle together to school. Children whose paths included heavily trafficked roads were accompanied by parents or older children.

Other behavioral factors we identified were the children's knowledge of the benefits of AST and their motivation to engage in behavior change. To further improve the program, the next step involved collecting the children's ideas on how to develop the program, as well as increasing their knowledge and motivation through workshops. The workshops had 3 different themes: (1) health and how physical activity affects the body and mind, (2) transportation safety (especially concerning bicycling and bullying), and (3) environmental effects of AST. The knowledge the children gained during the workshops was later used in the intervention period during standard school lessons. The workshops lasted for approximately 45 min, and information and discussions were mixed together. Examples of schoolchildren's ideas on how to develop the program included encouraging pep talks within the pairs to increase AST use. Moreover, the children and their teachers worked collaboratively to divide the children into small groups or pairs according to

where their homes were situated, constituting an empowerment approach.

To further enhance the children's motivation to use AST, the program used gamification elements. Every day during the 4-week test period, the children put a sticker on a collective board for every kilometer they walked or bicycled between home and school, and the board's results were integrated into lessons. For example, Mathematics class was integrated with Geography class, and the children summed the total number of kilometers achieved each week, converted kilometers into miles, and identified the locations on a map. In our previous research, we found that measuring physical activity was an effective part of a school-based intervention, and this motivated adolescents to be more physically active [33].

Another gamification element was special assignments (a challenge) that the children were encouraged to solve each week. The teachers selected the assignments, which were directly connected to the curriculum. One of the assignments on the first week was, "Which traffic signs do you encounter on your way to school?" The assignments were integrated throughout the curriculum. For example, in the Art class, the children painted pictures of traffic signs. Another assignment during the week was a security check of the bicycles in which the children followed a checklist concerning legal requirements for bicycle equipment. The second week's special assignment was, "Count how many people you meet when walking or bicycling on your way to school," and this assignment was integrated into the Math class. The assignment for the third week was "Bring a plastic bag and collect some litter on your way to school." This assignment was used in a lesson concerning the environment in which the children learned about and practiced sorting litter into plastic, paper, etc. They also learned about what happens to animals and nature if the litter is left out in the environment. The fourth week's assignment was "Notice which signs of spring you encounter on your way to school," and this assignment was integrated into Biology class. Each Friday, the teachers summarized the assignment for the week, and a badge was awarded to the class for successful achievement.

Phase 3: Program Evaluation Plan and Implementation Plan

Developing a plan for the adoption, implementation, and sustainability of the program in real-life contexts began when the needs assessment was undertaken, as careful examination of the end users' needs contributed to program compatibility. To evaluate the program, we collected experiences from the children and teachers through focus groups. We used a semistructured interview guide to cover all aspects of the program. The opening question was "Let's pretend I know nothing. Could you please tell me about the program?" To expand upon the answers, follow-up questions were asked. Seven focus groups with 4 to 5 children in each group and one focus group consisting of the teachers were convened. The focus groups' discussions lasted for 16 to 45 min. Collectively, the 42 children walked or biked for 1189 km over 4 weeks, which averaged to 1.4 km for each child per school day. Bicycling contributed to at least 15 min of extra physical activity each day. The preliminary analysis of the focus groups showed that the students got motivated by the gamification elements of the intervention (ie, incorporating learning activities into assignments and measures of the use of AST), and they gained learning outcomes using time outside scheduled school hours. Furthermore, the teachers in this project found it highly rewarding to incorporate learning into AST because it made it possible to use real-life situations to teach various subjects in the curriculum.

In addition, before the intervention, we collected data on parental attitudes using the Modified Integrated model for Children's Active Commuting to School questionnaire, and the parents answered an open letter as well, which was introduced with the following text: "You have answered a questionnaire concerning AST, including obstacles your child might experience while using AST. Describe how these obstacles can be overcome." Two weeks after ending the intervention, a second open letter was introduced with 4 questions: "How have you as a parent experienced your child's participation in the AST project"; "If this project is used in a different class, is there something we should do again, and are there things that should be changed"; "Which attitude towards AST did you have before the intervention, and have your attitudes changed after participating"; and "Has your own choice of travel modes changed during the project?"

The knowledge gained from these data will provide important information on key program components, which will enable us to develop sustainable health-promoting programs in a school context. We have planned to implement this program in several schools, and after implementation, feasibility and efficacy studies using cluster randomization are planned.

Discussion

Principal Findings

In this paper, we describe the systematic development of an intervention program aimed at promoting AST among children. By following the steps of the IM process, it became evident that empowerment and gamification are 2 promising avenues to consider when designing AST interventions in a school context.

Using empowerment and engaging end users was essential. By forming a planning group that included important agents who control the environmental factors, it was possible to create a promising approach for developing a sustainable physical activity program in a school that could yield positive outcomes for children. In young children, parents are the gatekeepers and they decide whether the child will use AST or other means of transportation. Thus, it is essential to involve them in the process. However, this approach is unusual. A common theme that occurs in many school-based research articles is the lack of engagement by end users in planning, implementing, and evaluating health promotion activities [25,34]. Therefore, we anticipate that one success contributor for this program was the use of empowerment.

A second important cornerstone was the use of gamification, which made it possible to integrate learning and AST through the use of school assignments, including ones that incorporated measurements of AST usage. Preliminary finding showed that gamification motivated children to use AST, a finding that is supported by Hamari et al [35]. There is an ongoing debate within gamification research as to whether specific game elements may actually undermine users' intrinsic motivations [36]. A study examining the effects of 3 commonly employed game design elements (points, leaderboard, and levels) on users' performance and intrinsic motivation showed that these game elements significantly increased performance but did not affect intrinsic motivation. These findings suggest that points, levels, and leaderboards by themselves do not make or break users' intrinsic motivation in nongame contexts [36]. However, the use of gamification in schools must be further explored, as the relationship between the engaging aspect of games, learning, and physical activity is still unknown [37].

Future Work

By integrating learning activities into the project, schools may be more motivated to put time and effort into implementing this program. There are complex interactions among socioeconomic, environmental, and ethnic and cultural differences, and these may be important to account for when designing effective programs to promote children's AST. Future evaluation methods need to include a target group that displays a wider range of socioeconomic factors.

Conclusions

IM proved to be a valuable method to develop a structured intervention for an active school transporting intervention for children. By following the steps of the IM process, it became evident that empowerment and gamification are 2 promising avenues to consider when designing AST interventions in a school context. By engaging end users and including important agents, such as parents and teachers, who control the environmental factors, the possibility to design a sustainable program increases. In addition, gamification made it possible to integrate learning into AST, which could motivate schools to devote time and effort to implementing this program.

Acknowledgments

Authors' Contributions

Both AL and SR cooperated on the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and study supervision.

Conflicts of Interest

None declared.

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Abbreviations

AST: active school transportation
IM: Intervention Mapping

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Protocol

Design and Rationale for a Parent-Led Intervention to Increase Fruit and Vegetable Intake in Young Childhood Cancer Survivors (Reboot): Protocol for a Pilot Study

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Abstract

Background: Poor dietary habits are common among childhood cancer survivors, despite increasing their risk of cardio metabolic complications after cancer treatment. Here, we describe the design and rationale for a pilot telephone-based, parent-led intervention aimed at increasing fruit and vegetable intake in young cancer survivors (Reboot).

Objective: This pilot study aims to assess the feasibility and acceptability of delivering evidence-based telephone support to parents of childhood cancer survivors. A secondary aim includes assessing the effect of Reboot on improving childhood cancer survivors' dietary quality by increasing child fruit and vegetable intake and variety and its contribution to overall nutrient intake.

Methods: We aim to recruit parents of 15 young cancer survivors aged 2 to 12 years who have completed cancer treatment less than five years ago. The intervention comprises of 4 weekly 45-minute telephone sessions led by a health professional and one booster session 6 weeks later. Sessions address the effects of cancer treatment on children's diets, recommended fruit and vegetable intake for children, and evidence-based strategies to promote the consumption of fruit and vegetables as well as to manage fussy eating.

Results: Reboot is based on an existing, evidence-based parent nutrition intervention and modified for childhood cancer survivors following extensive collaboration with experts in the field. Primary outcomes of feasibility and acceptability will be measured by the number of participants who complete all five sessions, average session length (minutes), length between sessions (days) and parent Likert ratings of the usefulness and impact of the intervention collected after the booster session. Of the 15 participants we aim to recruit, 3 have completed the intervention, 1 declined to participate, 11 are actively completing the intervention and 2 participants are providing written consent. The remaining 3 participants will be recruited via telephone follow-up calls. The intervention is due to be completed by July 2018.

Conclusions: Reboot aims to support healthy dietary behaviors in childhood cancer survivors who are at increased risk of developing serious cardiometabolic complications after their cancer treatment. Results will inform the development and implementation of future evidence-based dietary interventions delivered to childhood cancer survivors, particularly those living in rural and remote areas.

Registered Report Identifier: RR1-10.2196/9252

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KEYWORDS

childhood cancer survivor; child, diet; feeding patterns; fruit; vegetables

Introduction

The cardiotoxic effects of chemotherapy and radiation have been shown to contribute to an increased risk of cardiovascular disease in survivors of childhood cancer [1]. Consequently, childhood cancer survivors (CCS) are more than six times more likely to experience serious cardiac conditions compared with their siblings, with rates continuing to increase as late as thirty years after cancer treatment [2].

One of the key predisposing factors for cardiovascular disease is metabolic syndrome, a cluster of conditions which includes central obesity, dyslipidemia, glucose intolerance and hypertension [3]. There is a strong association between a diet low in fruit and vegetables and high in saturated fat and sugar, and the onset of metabolic syndrome in CCS [4]. Consequently, CCS with metabolic syndrome are twice less likely to meet national dietary guidelines compared with those who do not have the syndrome [4].

Despite their increased risk of developing serious chronic health conditions, young CCS often report poor health-protecting behaviors [5-8] (eg, reduced intake of fruit and vegetables, excessive energy, and inadequate calcium and folate intake) [9] and a higher intake of non-core ("junk") foods compared with prediagnosis [10]. These behaviors often develop during treatment when children's home food environment and eating are disrupted by frequent hospital admissions and treatment related side-effects including nausea, increased appetite, and vomiting [11]. Unhealthy eating habits established during cancer treatment also appear to be exacerbated by parents of CCS who report using unhealthy food as a means to reduce children's pain and emotional distress after cancer treatment [10,11].

Although dietary behaviors are among the most easily modifiable factors for reducing the risk of cardio metabolic complications, CCS and their families often live long distances from their tertiary hospital [12] making it difficult for health professionals to provide ongoing nutritional support after treatment completion. Telephone interventions may therefore represent a feasible and acceptable approach for promoting healthy eating habits among CCS.

Telephone-based parent-led interventions have successfully increased fruit and vegetable intake in children not previously treated for cancer [13-17]. However, the feasibility and acceptability of telephone-based, parent-led fruit and vegetable interventions in CCS is yet to be evaluated. Therefore, we aim to assess the feasibility and acceptability of delivering evidence-based telephone nutritional support to parents of CCS.

Methods

Recruitment

We aim to recruit the parents of 15 CCS. This number is sufficient to provide exploratory findings to inform the design of a randomized controlled trial (RCT) in this population [18]. Based on our previous research, we assume a response rate of 50% and attrition rate of 20% [18-20], and therefore it was anticipated that approximately 50 parents will need to be contacted to recruit 15 families.

Parents will be eligible to participate if they have a child aged between 2-12 years who completed cancer treatment at the Sydney Children's Hospital (SCH), Randwick, NSW, with curative intent, achieved remission less than 5 years ago and meet the following criteria which are (1) to provide informed consent, (2) be able to read English, and (3) have regular telephone access. Parents will be ineligible if they have (1) insufficient English language skills to complete telephone sessions and or baseline and follow-up assessments, (2) severe depression or suicidal ideation, as determined by the clinical experience of the treating oncologist, or if their child who had cancer, (3) is currently on active treatment or receiving supplementary feeding, (4) has relapsed, (5) is in palliative care or is deceased, or (6) completed cancer treatment more than five years ago.

Eligible participants will be recruited via mail using an information and consent form explaining the purpose of the project and details of participation. Participants can choose to participate by returning the consent form or by contacting the study coordinator. Nonrespondents will be contacted by study personnel via telephone or text message. This protocol was approved by the Network Human Research Ethics Committee (HREC/15/SCHN/395).
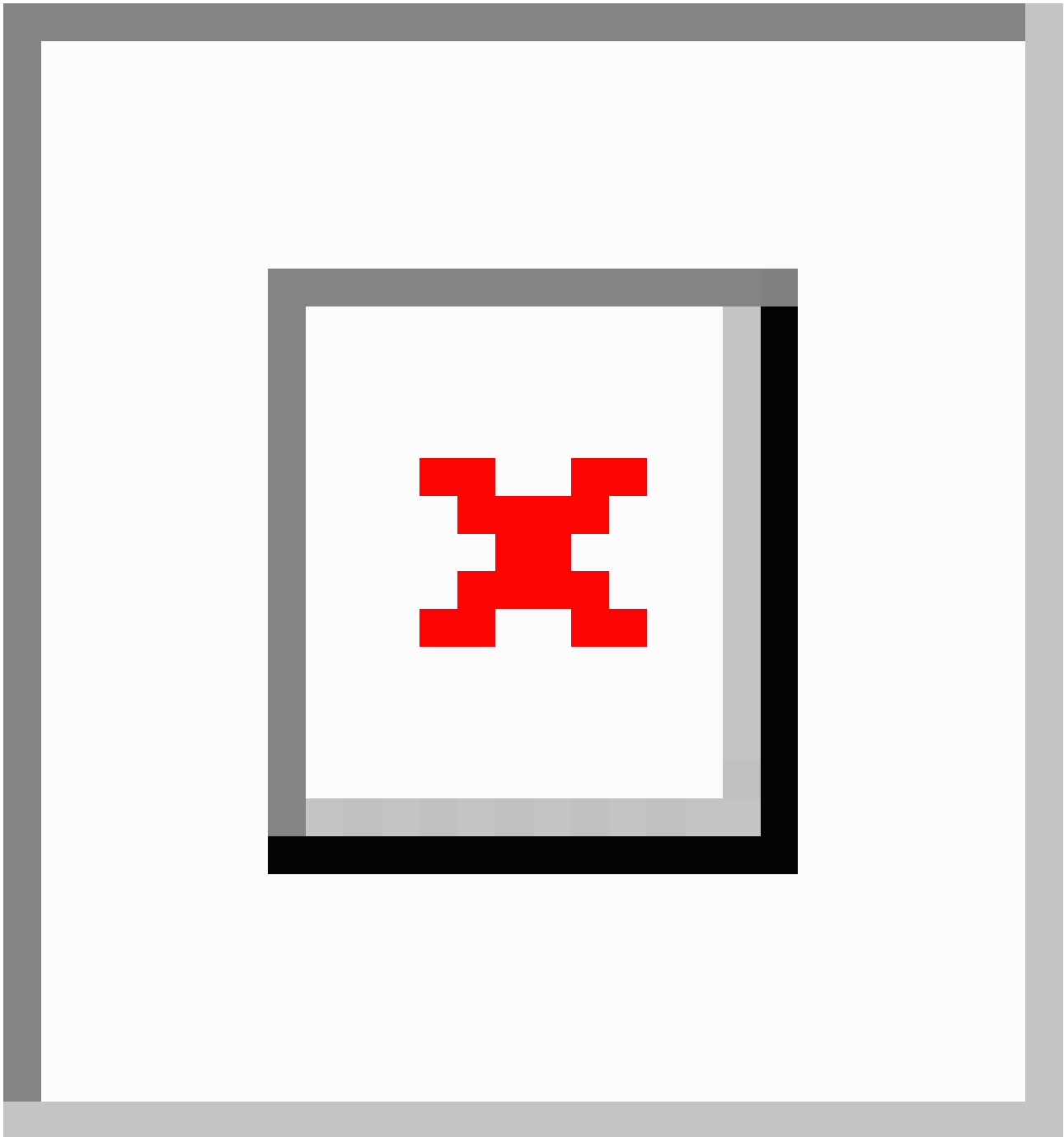
Intervention

Reboot models a previous intervention aimed at increasing fruit and vegetable intake in over 400 Australian children (who did not receive cancer treatment) [16]. Following a parent-led interventional model, the parent (not the child) receives the intervention and is responsible for regulating the home food environment and acting as an important role model, which maintains children's eating behaviors [21].

In line with the original intervention, Reboot will be delivered to only one parent by a trained health professional (either a registered psychologist or dietitian) via 4 weekly 45-minute telephone sessions, with the addition of 1 booster session 6 weeks after the fourth intervention session (Figure 1). Intervention sessions will be guided by a parent guidebook (Figure 2) focusing on key factors associated with increased intake of fruit and vegetables in children, including the accessibility of fruit and vegetables in the home, parental providing and modelling of fruit and vegetable intake, and positive family-based mealtime practices (eg, eating together) [22]. Further details are shown in Table 1.

Figure 1. Reboot Kids study flowchart.

Figure 2. Excerpts from the Reboot Kids parent workbook.
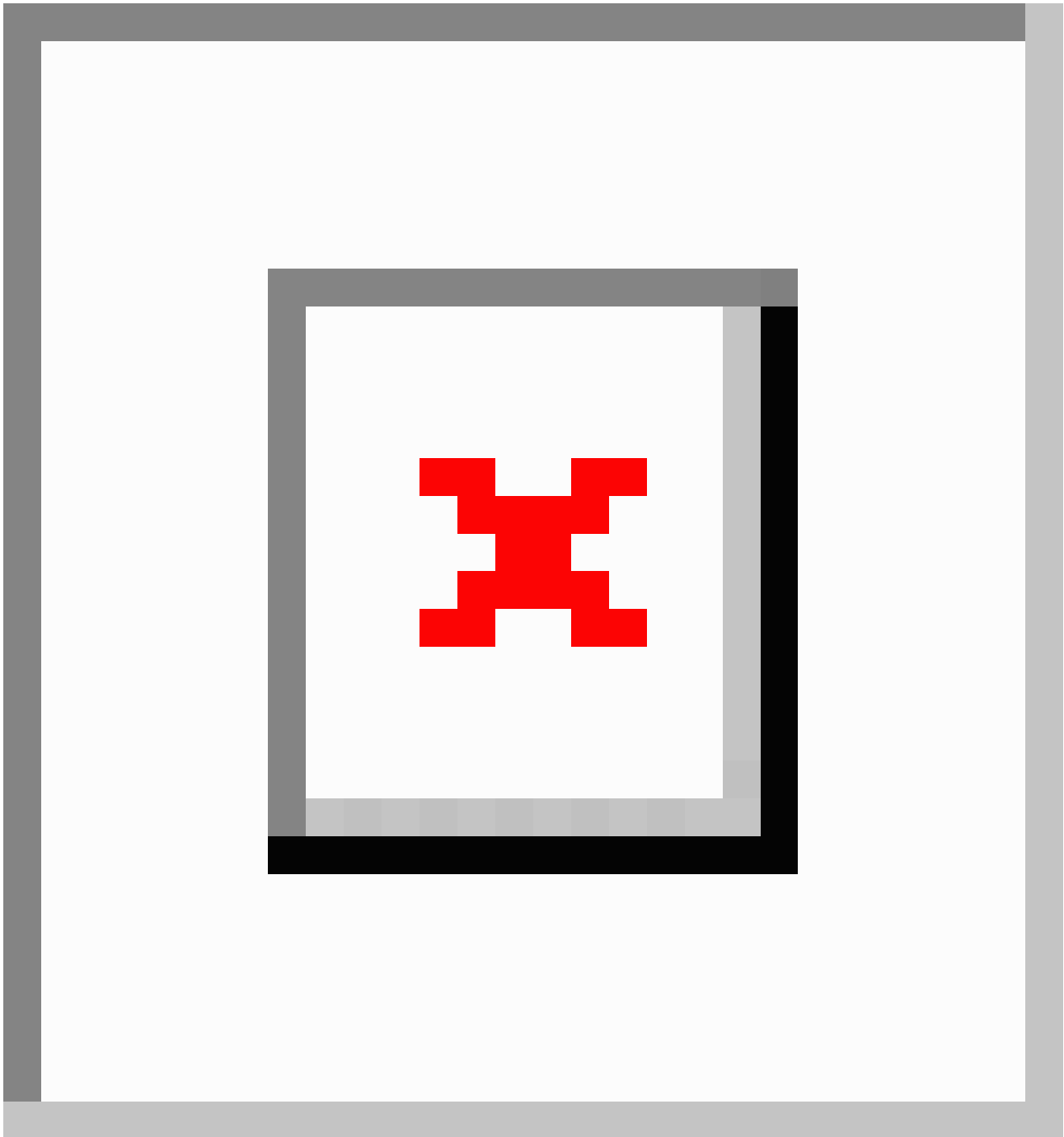
Table 1. Reboot intervention session objectives and cancer-relevant content (CCS: childhood cancer survivors).

Weekly session	Core objectives and skills	Cancer relevant content
Introduction and overview	• Understanding the rationale for intervening or eliciting motivation. • To promote mastery by normalizing parents' concerns and fears. • Understanding the Australian Guide to Healthy Eating and portion sizes. • Information about the type and quantity of fruits and vegetables that children should be eating. • Identify 'non-core' foods and strategies to reduce non-score food intake. • Understanding the importance of parent providing fruit and vegetables throughout the day. • Introduction of the parent vegetable providing diary to encourage parent self-monitoring of the number of occasions parents provide fruit and vegetables to children throughout the day. • Setting specific and achievable program goals.	• Importance of supporting healthy eating habits and regular physical activity after cancer treatment. • Common experiences of children and parents during and after cancer treatment (eg, food aversions, poor fruit and vegetable intake, altered taste perceptions, physical inactivity, and parent overprotectiveness). • End of cancer treatment is one of the most difficult times for families. • Addressing challenges (eg, effects of treatment on re-establishing a normal routine, including fatigue, fussy eating, inconsistent discipline, misbehavior, and overprotectiveness).
The home food environment	• Identify barriers to introducing change (establishing rules and coping with change). • Tips for structuring family mealtimes. • Providing praise and positive reinforcement. • Brainstorm effective non-food rewards. • Review strategies for creating a healthy home environment. • Introduce meal planning. • Plan for the week ahead.	• Addressing challenges for families establishing change after cancer (eg, parent guilt and or overprotectiveness, misbehavior resulting from absence of discipline, and routine during treatment).
Encouraging children to eat vegetables	• Practical strategies for promoting fruit and vegetables to children (eg, planning and providing choices). • Tips on making food exciting and interesting. • Preparing for misbehavior. • Discussion of unhelpful strategies (what to try and what to avoid). • Understanding the importance of role modelling healthy eating habits to children.	• N/A
Consolidation	• Review topics from the previous four weeks. • Strategies for shopping with children. • Review program goals. • Preparing for future challenges.	• Address any parent fears and or concerns moving forward.
Booster	• Review program goals and progress (eg, CCS fruit and vegetable intake, parent-providing, and role modelling of fruit and vegetable intake to CCS). • Introduce screen time guidelines. • Introduce sleep guidelines. • Harnessing support from family and friends.	• Re-addressing challenges for families establishing behavior change after cancer, including other caregivers

Treatment Late Effects

A study by our team identified a significant proportion (>90%) of Australian and New Zealand parents reporting unmet needs for information about the late effects of cancer treatment [23]. An introductory information module (*"Why is healthy eating important for children after cancer treatment?"*) was developed to increase parents' knowledge about the most common serious long-term health problems identified among childhood cancer survivors (eg, weight gain, heart disease, diabetes, high blood pressure, and high cholesterol) and evidence-based behaviors that may help to prevent or reduce occurrence of treatment late effects (eg, increasing children's intake of fruits and vegetables).

Changes in Parenting Behavior and Children's Eating Habits

The introductory module also includes an overview about why healthy eating is difficult for children and parents after cancer treatment. A summary of the six most common challenges is provided and it includes topics such as loss of appetite, taste changes, food aversions, steroids, limited exposure to new foods, and increased parental leniency for unhealthy foods and emotional feeding. A synopsis about common changes in children's eating habits after cancer treatment is also provided to normalize parents' experiences (eg, increased intake of junk foods and decreased intake of vegetables).

Following our modifications, the parent guidebook was assessed for readability using the Flesch-Kincaid Grade Level Test [24],

yielding a grade level test score of 7.6 or a seventh to eighth grade school level. In concordance with the Australian National Framework for Consumer Involvement in Cancer Control [25], parents of CCS (N=4) were involved in reviewing the guidebook and providing feedback prior to publication.

Primary and Secondary Outcome Measures

Demographic Information

Information on parent sex, age, education and employment status will be collected at baseline (T1, see Figure 1) together with the sex and age of the CCS. A validated emotion thermometers tool will also be used to assess participant distress and emotional state at the start of each intervention session [26]. This tool individually screens for emotional upset, anxiety, depression, and anger by asking the participant to rate each emotion on a scale of 0-10 (where 0 is none and 10 is extreme), and the level of assistance required to manage these emotions [26]. A participant will be deemed "distressed" if they score above seven on any of the thermometers [20], requiring facilitators to enquire about the participants available psychological supports (eg, current psychologist, general practitioner [GP], or social worker), and, if needed, will provide information for appropriate services including a 24-hour crisis hotline. The chief investigator will be contacted, and a nominated health professional will be contacted with the participant's consent if appropriate.

Feasibility and Acceptability

Feasibility will be assessed using several descriptive indices. These include the number of participants who complete all 5 intervention sessions (participation rate), average session length (minutes), and days between sessions. To evaluate the ease, usefulness, and impact of the intervention (see Textbox 1), participants will be invited to complete and online survey after the fourth intervention session (T2, Figure 1) to rate their agreement on several acceptability items using a 5-point Likert scale from strongly disagree to strongly agree (eg, "*The Reboot program improved my knowledge about strategies for promoting fruits and vegetables to my child*"). Items from the task and goal subscales of the Validated Working Alliance Inventory were also included to evaluate participants perceptions of the facilitator (eg, competence) [27].

Childhood Cancer Survivors Fruit and Vegetable Intake

To measure CCS fruit and vegetable intake, participants will be invited to complete 2 validated dietary intake assessment methods at baseline (T1), after the fourth intervention session (T2) and 6 months after the fourth intervention session (T3) (see Figure 1). These measures will include the following aspects listed below.

24-hour Dietary Recall

A 24-hour dietary recall will be conducted by a registered dietitian via telephone [28] to obtain a list of everything the CCS ate and drank during the previous day. This information will be manually entered into FoodWorks 8, an Australian nutrient analysis software (Xyris, Brisbane, QLD, Australia), by a registered dietitian to produce a calculation of total daily fruit and total daily vegetable servings for each child [29]. Intake (total fruit and total vegetable servings consumed) will also be used to categorize CCS as meeting (or not meeting) the recommended daily intake for fruit and vegetables, separately, for their age.

Food Frequency Questionnaire

The fruit and vegetable subscales scores from the Australian Child and Adolescent Eating Survey, a brief (15 minutes) online FFQ, will be used to provide quantitative data on the number of daily fruit and vegetable serves for age and variety of fruit and vegetables consumed [30-32] where a higher fruit (out of 12) and vegetable variety score (out of 21) indicates greater intake of a variety of fruit and vegetables [33].

Statistical Analyses

Data will be analyzed using the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc, Chicago, IL, USA). The primary outcome measure (number of participants who complete all 5 intervention sessions) will be analyzed using a repeated measures design. An 80% study compliance and 20% attrition rate [18] will be used as the benchmark for program feasibility. Cochran Q will be used to identify participants as meeting the specific study completion criterion. The secondary outcome measure is the difference in the mean number of fruit and vegetable serves consumed by CCS (on the previous day) from baseline to the end of the intervention (after the booster session). Paired *t*-tests will be conducted to determine whether there is a significant difference between the mean intakes of fruit and vegetable serves at baseline compared to the end of the intervention.

Textbox 1. Postintervention Acceptability Items.

Skills and confidence

- The skills I learnt in Reboot Kids have been useful in increasing my child's fruit and or vegetable intake.

- The home practice activities have helped me to put these skills into practice.

- I feel more confident in managing my child's eating habits.

- The Reboot program helped to me recognize the importance of healthy eating habits for children after cancer treatment.

Telephone sessions

- I found the number of telephone sessions was about right.

- I would have preferred more than four telephone sessions.

- I would have preferred less than four sessions.

- I found the telephone sessions to be inconvenient.

- I found the telephone sessions to be easy to understand.

- I found the telephone sessions to be personally relevant.

- I found the telephone sessions to be useful.

- I found the telephone sessions to be too long.

Information

- I was satisfied with the amount of information in Reboot.

- I was satisfied with the quality of information in Reboot.

- I was satisfied with the amount of information in Reboot.

Parent workbook

- I found the parent workbook easy to read.

- I found the parent workbook useful.

- I will continue to use the parent workbook after the program has finished.

- The resources provided in the parent workbook were useful.

Telephone vs online

- I was satisfied with receiving Reboot over the telephone.

- I would have preferred to complete Reboot online.

- I would have preferred to complete Reboot online with some telephone support.

- I would have preferred to complete Reboot by myself in my own time.

Questionnaires

- The Reboot questionnaires were too long.

- The Reboot questionnaires were too frequent.

Overall

- I enjoyed participating in Reboot.

- I would recommend Reboot to other families.

Results

Initial planning for Reboot Kids began in 2015 via a collaboration with the developers of the 'Good for kids: Healthy Habits program' at the University of Newcastle [15]. Healthy Habits is an evidence-based fruit and vegetable program delivered to nearly 400 Australian families. With their consent, our team updated the original parent guidebook to include the most recent version of the Australian Dietary Guidelines and Nutrition Australia Healthy Eating Pyramid, and dietitian approved recipes. To promote immediate and long-lasting intervention changes, we also followed recommendations by the original developers to focus on parent providing of fruit and vegetables to CCS, which mediated the short-and-long-term

effectiveness of the intervention [22]. We therefore modified the initial behavior change technique from parenting self-monitoring of CCS daily fruit and vegetable intake to occasions of parent providing of fruit and vegetables to CCS over three days (Table 1).

Ethics approval was obtained on 11th November 2015 (HREC/15/SCHN/395) and recruitment commenced in August 2016. Of the 20 participants we aim to recruit, 7 have completed the intervention (including the booster session), 1 declined to participate after consenting, 2 participants dropped out after completing the first session, 8 are actively completing the intervention and 3 participants are providing consent. We aim to recruit the remaining participants via telephone follow-up calls and complete the intervention by July 2018.

Discussion

This paper outlines the protocol for a pre-post, parent-led behavioral nutrition intervention for CCS, previously evaluated in a non-cancer pediatric population [15,16]. Although interventions piloted in non-cancer pediatric populations have led to significant increases in child fruit and vegetable intake [16], there is no research on their effectiveness in this high-risk population of CCS [34]; highlighting the unique contribution of the Reboot program [35].

We anticipate that the multimodal approach used in Reboot, encompassing a written parent guidebook and semi-structured telephone calls will contribute to the aim of the study. Telephone contact as the primary mode of intervention delivery can be efficacious [36], providing parents with support from a healthcare professional without requiring travel [12]. This flexibility is important in ensuring equitable access to families of CCS living in rural and regional areas [12]. Parents of CCS also report a preference for workbooks which provide relevant information about their children's health after treatment [12].

The number of intervention contacts is also known to moderate intervention effectiveness, with behavior change often requiring multiple points of contact [37]. Booster sessions are often recommended to reinforce or re-establish messages or behavior changes suggested during interventions [38]. Subsequently, we chose to modify the original intervention to include 1 booster session. However, there is no research on the impact of booster sessions in dietary interventions in CCS. Moreover, the effectiveness [38] and optimum timing [39] of booster sessions

in the wider behavior change literature is also unclear [40]. Most studies suggest that booster sessions should be instituted within three months after the intervention is complete to maximize efficacy [38,39], supporting our design of a booster session at 6 weeks post-intervention.

The Reboot study design has both strengths and limitations. As a pilot study, the small sample size will limit the ability to draw definitive conclusions regarding the efficacy of the intervention in increasing fruit and vegetable intake among CCS. The study will, however, be most useful in assessing the feasibility and acceptability of delivering a behavioral nutrition intervention in this population (Textbox 1). The inherent vulnerabilities of using parent-report as a proxy for child intake also warrants consideration [41]. A recent study indicated that repeated 24-hour recalls were a more valid measurement of dietary intake in CCS compared with FFQs, which underestimated energy intake [28]. However, due to the participant burden of multiple 24-hour recalls [42], we aimed to reduce potential bias in intake measurement by using a single 3-pass 24-hour recall and a validated, parent-administered online FFQ.

The increasing use, and success, of technology-based, parent-led interventions in improving children's fruit and vegetable intake [43] suggests that online or smart-phone delivered interventions may offer a cost-effective alternative to telephone-based behavior change support [44-46]. Alternatively, online or mobile phone interventions delivered together with minimal telephone support or text messaging, may also help to maintain important human interaction [47] whilst still reducing intervention delivery costs. Given the absence of evidence-based dietary interventions in CCS [48], experimentation with different modes of delivery is an important next step in identifying the most efficacious method for promoting healthy eating habits in this vulnerable population [47].

Subsequently, a future goal of this pilot study is to utilize our feasibility and acceptability data to inform the development of a randomized control trial to evaluate the efficacy of delivering reboot online via web-based modules with brief telephone support (15 minutes) to reinforce key messages, on CCS dietary intake, compared with a wait-list control. If successful, data obtained from the RCT will be used to support the implementation of Reboot by community organizations across Australia, especially those in rural and remote areas, where CCS have poorer access to preventive health care [49].

PG for her assistance with formatting of the manuscript and to consumer representatives for their invaluable feedback on the usefulness, ease of use, and appeal of the workbook (Barry Sharkey, Maria Messina and Carolyn Blakemore).

Authors' Contributions

Conflicts of Interest

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Abbreviations

CCS: childhood cancer survivors
FFQ: food frequency questionnaire
RCT: randomized controlled trial
SCH: Sydney Children's Hospital, Randwick

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Protocol

Confocal Laser Endomicroscopy and Optical Coherence Tomography for the Diagnosis of Prostate Cancer: A Needle-Based, In Vivo Feasibility Study Protocol (IDEAL Phase 2A)

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Abstract

Background: Focal therapy for prostate cancer has been proposed as an alternative treatment to whole-gland therapies in selected men to diminish side effects in localized prostate cancer. As nowadays imaging cannot offer complete prostate cancer disease characterization, multicore systematic biopsies are recommended (transrectal or transperineal). Optical imaging techniques such as confocal laser endomicroscopy and optical coherence tomography allow in vivo, high-resolution imaging. Moreover, they can provide real-time visualization and analysis of tissue and have the potential to offer additive diagnostic information.

Objective: This study has 2 separate primary objectives. The first is to assess the technical feasibility and safety of in vivo focal imaging with confocal laser endomicroscopy and optical coherence tomography. The second is to identify and define characteristics of prostate cancer and normal prostate tissue in confocal laser endomicroscopy and optical coherence tomography imaging by comparing these images with the corresponding histopathology.

Methods: In this prospective, in vivo feasibility study, needle-based confocal laser endomicroscopy and optical coherence tomography imaging will be performed before transperineal template mapping biopsy or radical prostatectomy. First, confocal laser endomicroscopy and optical coherence tomography will be performed in 4 patients (2 for each imaging modality) undergoing transperineal template mapping biopsy to assess the feasibility and safety of confocal laser endomicroscopy and optical coherence tomography. If proven to be safe and feasible, confocal laser endomicroscopy and optical coherence tomography will be performed in 10 patients (5 for each imaging modality) undergoing radical prostatectomy. Confocal laser endomicroscopy and optical coherence tomography images will be analyzed by independent, blinded observers. Confocal laser endomicroscopy– and optical coherence tomography–based qualitative and quantitative characteristics and histopathology will be compared. The study complies with the IDEAL (Idea, Development, Exploration, Assessment, Long-term study) stage 2a recommendations.

Results: At present, the study is enrolling patients and results and outcomes are expected in 2019.

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Conclusions: Confocal laser endomicroscopy and optical coherence tomography are promising optical imaging techniques that can visualize and analyze tissue structure, possible tumor grade, and architecture in real time. They can potentially provide real-time, high-resolution microscopic imaging and tissue characteristics of prostate cancer in conjunction with magnetic resonance imaging or transrectal ultrasound fusion-guided biopsy procedures. This study will provide insight into the feasibility and tissue-specific characteristics of confocal laser endomicroscopy and optical coherence tomography for real-time optical analysis of prostate cancer.

Trial Registration: ClinicalTrials.gov NCT03253458; https://clinicaltrials.gov/ct2/show/NCT03253458 (Archived by WebCite at http://www.webcitation.org/6z9owM66B)

Registered Report Identifier: RR1-10.2196/9813

Introduction

Prostate cancer (PCa) is the leading noncutaneous cancer in men and the third cause of cancer-related death [1]. To date, patients with a clinical suspicion of PCa, based on elevated serum prostate-specific antigen (PSA) and/or suspicious digital rectal examination (DRE), are recommended to undergo transrectal ultrasound (TRUS; +/− multiparametric magnetic resonance imaging, mpMRI)–guided systematic biopsies [2]. This work-up for PCa diagnosis carries some important drawbacks. Due to the heterogeneous nature of PCa, this procedure has a known risk of missing PCa lesions or underestimating PCa aggressiveness, besides overdiagnosis of insignificant lesions [3,4]. In the last decade, the diagnostic pathway for PCa has, therefore, moved more and more into imaging-based targeted biopsies instead of random systematic biopsies. Reliable prostate imaging is key for the reduction of unnecessary biopsies, insignificant PCa detection, increasing detection of significant PCa, reducing the number of cores, and to facilitate monitoring during active surveillance. Moreover, reliable imaging would play a pivotal role in treatment planning, and monitoring of focal treatment for low- to intermediate-risk localized PCa [5-8]. Especially, mpMRI of the prostate has evolved as an increasingly appealing tool in the PCa diagnostic armamentarium and is recommended in men with suspicion of PCa following a negative initial biopsy, and currently, it is even proposed to select patients for biopsies [2,5]. For focal therapy, in which the aim is to target treatment of significant disease with minimal toxicity, accurate disease identification, localization, demarcation, and grading of a lesion are essential. Focal therapy selection with mpMRI-targeted biopsies may be an option in experienced hands, but to date, there is a substantial proportion of false positives in lesions 3/5 or 4/5 scored with the prostate imaging reporting data system (PI-RADS) [9]. Moreover, the assessment of mpMRI-negative areas or the prostate as a whole using a transperineal prostate mapping biopsy using a template-guided approach is recommended [2,10,11]. Transperineal template mapping biopsies (TTMB) are able to sample the prostate at every 5 mm, and coordinates are correlated to the tumor location. Limitations of this procedure are the large numbers of cores needed per prostate, the rate of urinary retentions, and the operating room time with

its accompanying hospital admission [12,13]. Moreover, pathologists face a substantial increase in workload with a high number of biopsies, which often turn out to be benign.

Optical imaging technologies offer real-time imaging with excellent spatial and temporal resolution and are easily integrated into the operating room. In conjunction with mpMRI/TRUS-fusion image targeted biopsy, these real-time technologies in a needle-based form could provide valuable information for tissue characteristics. Adding real-time, in vivo diagnostic information of prostate tissue structure and architecture to already known information could improve PCa disease characterization. Optical imaging has the potential to make the diagnostic procedure less invasive, speed up the pathway, and reduce the currently existing workload of histopathological analysis.

Two optical imaging techniques currently used for needle-based optical biopsies are confocal laser endomicroscopy (CLE) and optical coherence tomography (OCT) [14-17]. CLE and OCT differ in background technology and image geometry and, therefore, show different images of the scanned tissue, see Figures 1 and 2.

CLE uses low-power laser bundles in a fiber optic probe, which can be inserted into the lumen of a needle to obtain real-time microscopic images of the tissue that is investigated. Backscattered light, from one specific tissue plane, is focused through a pinhole, whereas the backscattered light from surrounding tissue is rejected. This leads to high-resolution imaging of one specific plane of tissue in focus. The fluorescent light originates from the fluorescent dye nested in the extracellular matrix after topical or intravenous application. The most commonly used fluorescent dye is fluorescein. CLE is under investigation for gastrointestinal, urothelial, and pulmonary diseases, whereas for PCa, so far, only one study on CLE has been reported [14,18-20]. Lopez et al performed CLE during robot-assisted laparoscopic prostatectomy (RALP) in 21 patients to investigate the ability of CLE to assess surgical margins and nerve tissue with promising CLE-based characteristics of prostatic and periprostatic tissue [20]. In addition, no adverse events were reported related to the CLE procedure. However, these authors did not assess the ability to differentiate malignant from benign prostate cells.

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OCT is the optical equivalent of ultrasound imaging, based on the backscattering of near-infrared light. Flexible OCT probes, which can be inserted into a needle lumen, enable side looking real-time imaging with an axial resolution up to 10 μm and an effective penetration depth of around 2 mm [21]. Cross-sectional images are generated using an automated pullback system while the probe is rotating a small laser light bundle over the tissue. Within urology, OCT has been applied in evaluating malignancy of bladder, upper urinary tract, kidney, testes, and prostate lesions [22]. In PCa, OCT has been applied for intraoperative identification of neurovascular bundles, surgical margins, and extracapsular extension with the goal to preserve patient's functional and oncological outcomes [23-26]. A limited number of studies have looked at OCT's diagnostic role in differentiating benign and malignant microscopic tissue of the prostate gland. Muller et al demonstrated with the use of a histopathologic validation tool that ex vivo needle-based OCT measurements of radical prostatectomy specimens could differentiate between

cancer and healthy prostate tissue [27-29]. The quantitative analysis of the OCT signal by means of the attenuation coefficient was significantly higher in malignant compared with benign tissue with an area under the curve ranging from 0.64 to 0.89 depending on the histopathological analysis used [29].

The development of CLE and OCT toward real-time optical biopsies of prostate carcinoma may lead to advances in diagnosis and (focal therapy) treatment. Following phase 2a of the IDEAL criteria [30], we have separated the study protocol into 2 sequential aims with different procedures.

Procedure 1 aims to evaluate the technical feasibility of needle-based in vivo imaging with CLE and OCT in the prostate.

Procedure 2 aims to describe characteristics to be used for PCa detection, which allows us to create an atlas of CLE and OCT characteristics of normal and malignant prostate tissue based on a one-to-one comparison with histology.

Figure 1. Two examples of confocal laser endomicroscopy (CLE) images with Cellvizio AQ-flex 19 probe of ex vivo prostate tissue soaked in fluorescein solution for 2 min.
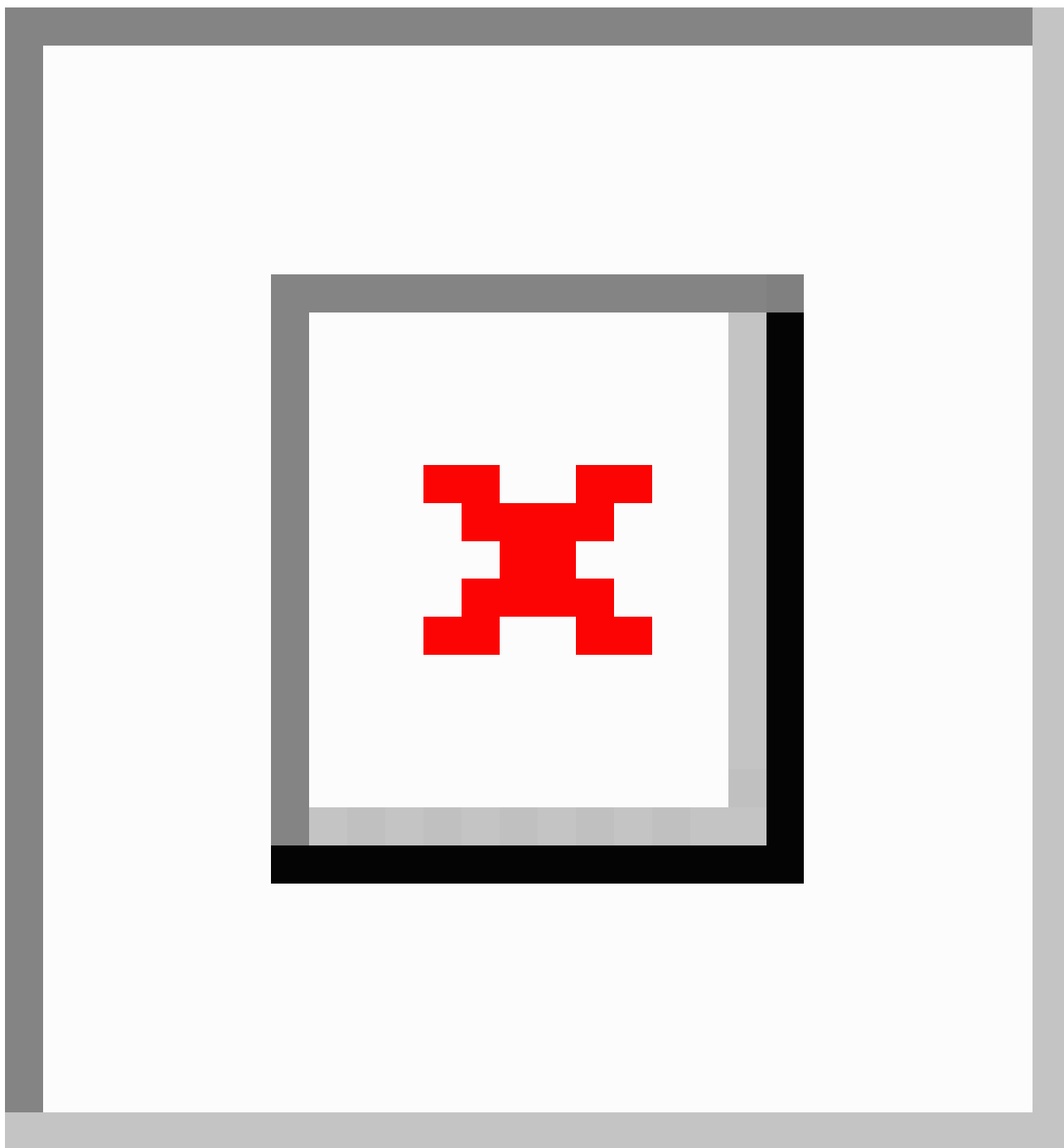
Figure 2. One b-scan of fixated ex vivo prostate tissue visualized with optical coherence tomography (OCT) with C7-XRtm Imaging System interfaced to a C7 Dragonflytm Imaging Probe (St. Jude Medical, St. Paul, Minnesota, USA).
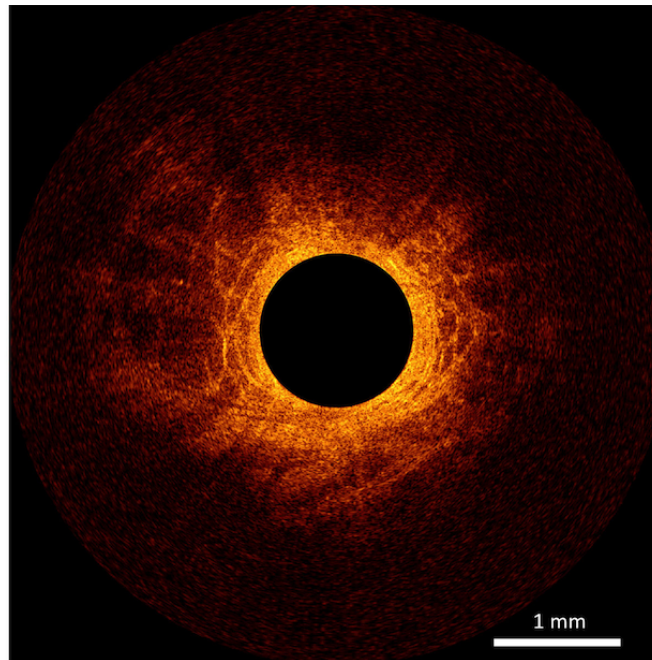
Methods

Study Objectives

The objective of procedure 1 is to assess the technical feasibility and safety of in vivo, needle-based, focal imaging of prostate tissue with CLE and OCT.

Procedure 2 has as primary objective to identify and define characteristics of PCa on CLE and OCT images. The secondary objectives are to correlate CLE and OCT images with histopathology, to develop an in vivo CLE and OCT image atlas of the prostate, and to assess procedure-related adverse events. The atlas will differentiate prostate tissues including benign glands, cystic atrophy, regular atrophy, stroma, inflammation, fat as well as different grades of malignant tissue using the Gleason score. The procedure-related adverse events will be evaluated using the Common Terminology Criteria for Adverse Events.

Study Design

This study is an investigator-initiated, multicenter, prospective in vivo feasibility study, using in vivo needle-based imaging methods with CLE and OCT. Approval of the local institutional review board (IRB) has been obtained for the study protocol under registry number: NL57326.018.17 on July 7, 2017, and the study was registered on the clinicaltrials.gov database (NCT03253458) on August 18, 2017. Any amendments to the trial protocol will be submitted for review by the IRB. Trial registrations will be updated, and participants will be informed about the risks and benefits of participation both verbally by one of the investigators and in writing in the form of an extensive patient information brochure. Participants will only

be included after written informed consent has been obtained. Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent (medical) reasons. Patient data will be anonymized and stored in a secure database.

The study design consists of 2 sequential procedures. CLE images are recorded with the AG-Flex 19 fiber optic mini probe-based system (Cellvizio System, Mauna Kea Technologies, Paris, France) with an outer diameter of 0.9 mm, a field of view of 325 μm, and a resolution of 3.5 μm. OCT images are recorded with a small rotating C7 Dragonfly Imaging Probe using the Light Lab OCT system (St. Jude Medical, Saint Paul, Minnesota, USA). Both devices and probes are illustrated in Figure 3.

For CLE imaging, a fluorescent contrast agent is needed to stain the extracellular matrix. Fluorescein (fluorescein sodium, Fresenius Kabi, Zeist, the Netherlands), a nontoxic and commonly used fluorescent dye, will be administered intravenously through an intravenous cannula [31]. Two times a bolus of 2.5 mL of 10% sodium fluorescein will be administered, one bolus per CLE measurement. The probes are transperineally introduced through a 17-gauge needle under ultrasound guidance. CLE images are recorded at a scan rate of 12 frames per second during a push and scan technique after placing the probe in direct contact with prostate tissue.

The OCT probe will be placed with a trocar needle in the prostate tissue under ultrasound guidance. After removal of the trocar needle, the inner part of the probe, the laser lens system is automatically pulled back while it is rotating, which creates a 3D image of the tissue.

Figure 3. A: Cellvizio CLE system, B: Cellvizio confocal Miniprobe (AG-Flex 19) through the 17-gauge introducer needle, C: St. Jude Lightlab optical coherence tomography (OCT) system, D: St. Jude OCT probe with a 0.9 mm diameter.
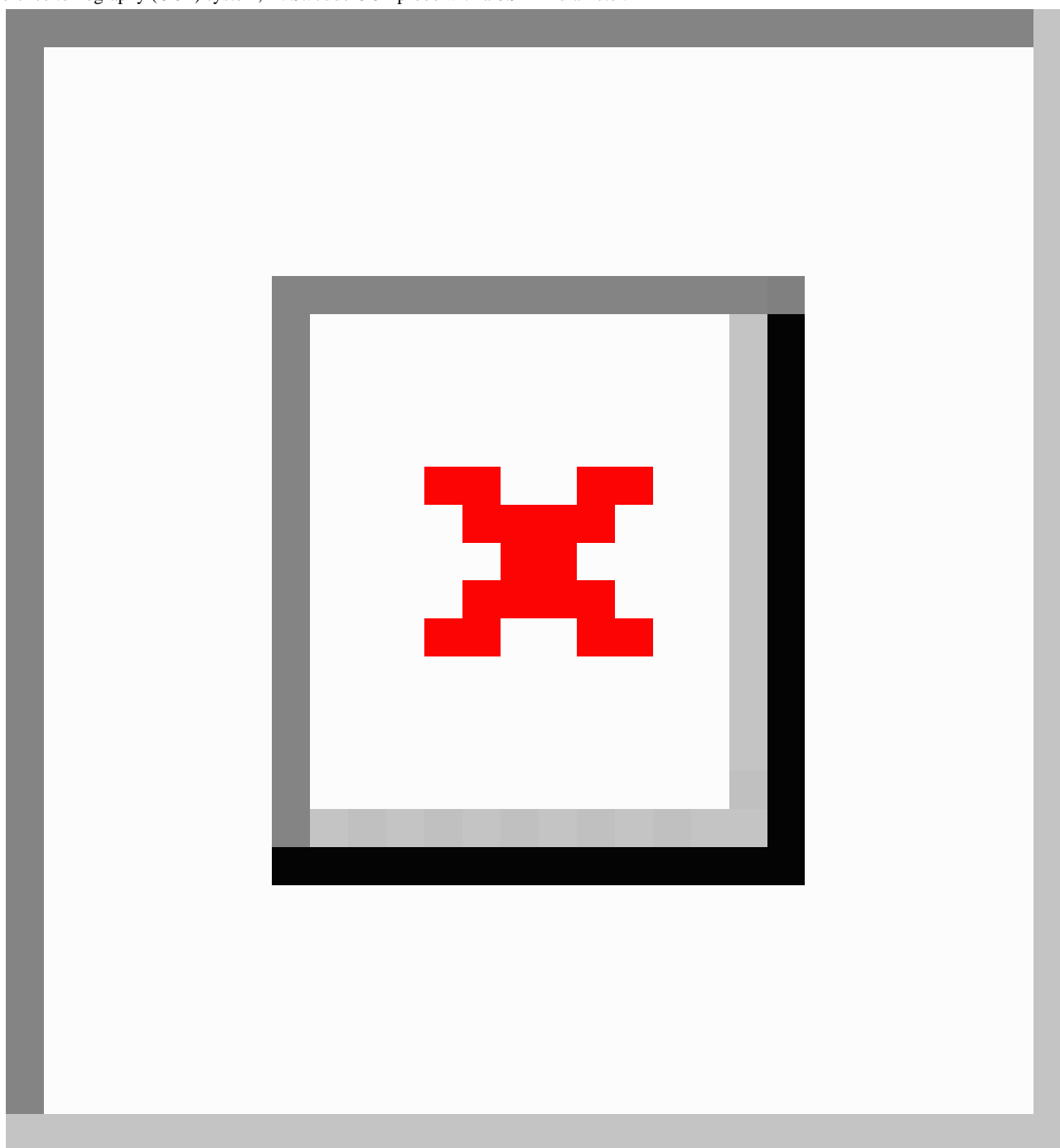
In procedure 1, patients scheduled for TTMB will undergo in vivo CLE or OCT imaging, before colocalized biopsy for standard histopathological assessment.

If it is shown in procedure 1 that in vivo CLE and OCT imaging are technically feasible and safe to perform, then procedure 2 will be initiated. In procedure 2, patients scheduled for RALP will undergo in vivo CLE or OCT imaging during surgery, before prostate removal. In general, 2 recordings of 90 s each will be made for the per-patient chosen modality. Recorded CLE and OCT imaging will be analyzed, at a later stage, by blinded independent observers and compared with the corresponding histopathologic evaluation of the prostatectomy specimen. Histopathological analysis is performed according to the standard clinical protocol and will be performed by a uropathologist, blinded for OCT and CLE imaging results. The uropathologist will, next to the standard examination procedure, perform a detailed reporting method; prostate tissue will be analyzed and annotated for various structures (benign glands, cystoid atrophy, regular atrophy, stroma, malignant tissue using the Gleason score, inflammation, and fat) on the whole mount histology slice or biopsies specimens. Histopathology is correlated with CLE and OCT data in a 3D computer environment. Adverse events are registered with a follow-up of 30 days.

Population

Patients (aged ≥18 years) who are indicated for a TTMB will be included for study procedure 1. All patients will be recruited in the AMC Hospital (Amsterdam, the Netherlands), and all study procedures will be performed in this institution. A total of 14 patients will be included in this study (Figure 4). Four patients will be included for procedure 1, 2 patients for optical imaging with CLE, and 2 with OCT. For procedure 2, 10 patients scheduled for RALP will be included, 5 of these patients will be imaged by CLE, 5 patients by OCT. Patients will be recruited in the AMC Hospital and VU Medical Center (Amsterdam, the Netherlands), and study procedures will be performed in both institutions. To increase the focal targeting of a PCa lesion, patients included in procedure 2 should have prostate mpMRI data available before the RALP with a visible (>5 mm) and suspect (PI-RADS v2: ≥3) region of interest. The other inclusion and exclusion criteria are listed in Textboxes 1 and 2, respectively. These sample sizes are based on prior publications and comply with the IDEAL 2a recommendation: low number of selected patients [29,30,32].

Study Procedures

Procedure 1: Transperineal Template Mapping Biopsy (4 Patients, 2 Confocal Laser Endomicroscopy Imaging and 2 Optical Coherence Tomography Imaging)

The standard TTMB protocol is performed using local spinal or general anesthesia, and patients are positioned in the lithotomy position. Hereafter, the biopsy stepper is placed using a stabilizer and table mount. A clinical ultrasound scanner (HI VISION Preirus, Hitachi Medical Systems, Japan) with the biplanar probe (EUP-U533, Hitachi Medical Systems, Japan) and the endocavity balloon is used. After transrectal probe placement, dimensions and prostate volume are measured including checking of the pubic arch interference. The perineum is cleaned for surgery and draped. A sterile, disposable (brachy) template grid, consisting of rows and columns with holes spaced 5 mm apart, is used to guide the imaging probe/biopsy needle. The optical imaging acquisition is then started. As the CLE measurement technique differs from the OCT measurement technique; both techniques are described separately below. The measurement trajectories will be mapped with the ultrasound console. A corresponding biopsy will be taken following the same trajectory as the focal imaging technique (CLE or OCT). When the CLE or OCT measurements are performed, the standard biopsy cores will be taken, and the procedure is finished. Flowchart of procedure 1 is displayed in Figure 5.

Figure 4. Study design, procedure 2: robot-assisted laparoscopic prostatectomy (RALP) will only start after a positive outcome of procedure 1: transperineal template mapping biopsy (TTMB). CLE: confocal laser endomicroscopy; OCT: optical coherence tomography.
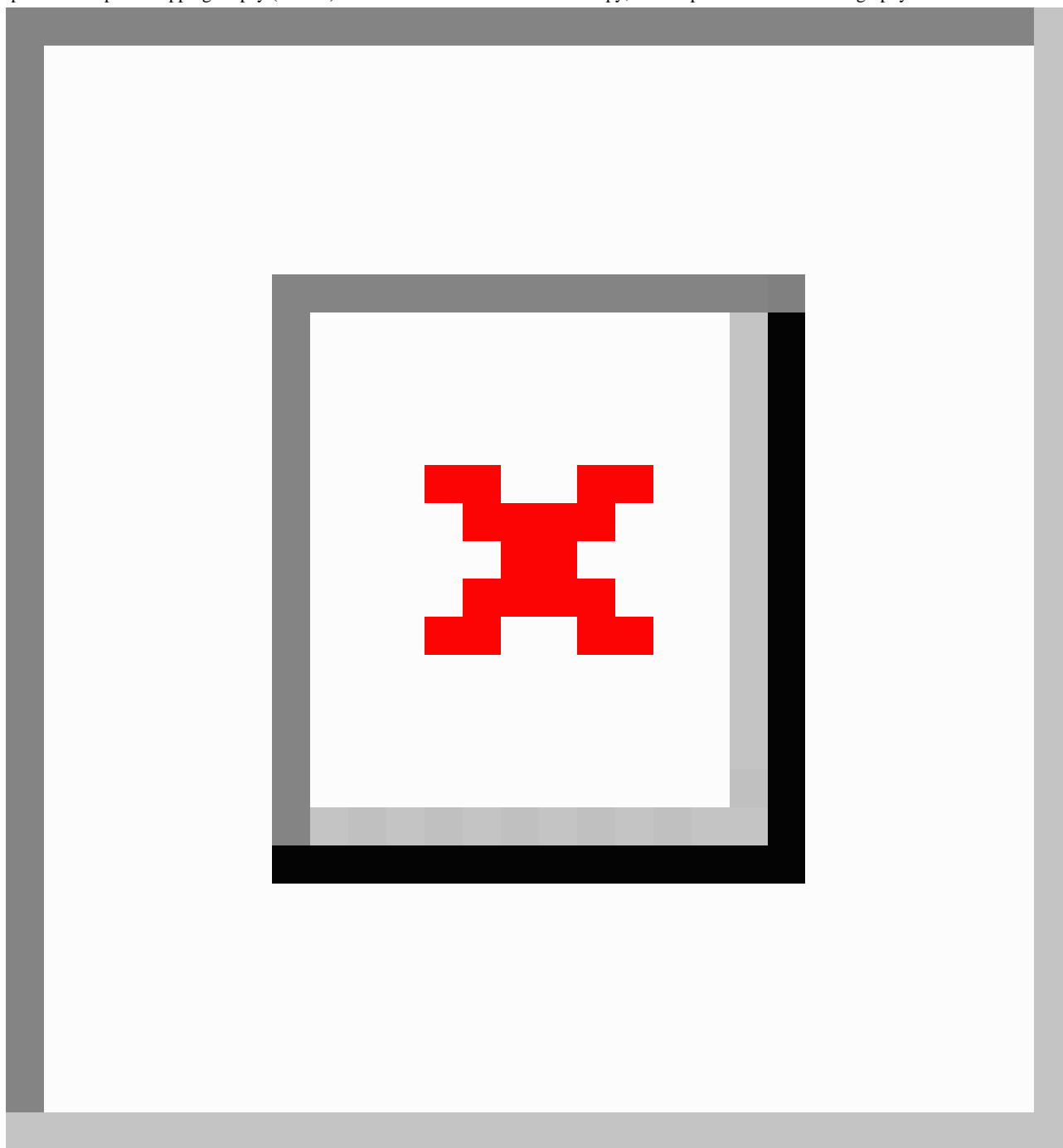
Textbox 1. Inclusion criteria.

To be eligible to participate in this study, a subject must meet all of the following criteria:
• Age ≥18 years
• Signed informed consent
• Multiparametric magnetic resonance imaging data are available (only for procedure 2)
• Visible (≥5 mm diameter) and suspect (prostate imaging reporting and data system, PI-RADS v2: ≥3) region of interest (only for procedure 2)

Textbox 2. Exclusion criteria.

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients with a known allergic reaction to fluorescein

- Documented acute prostatitis or untreated urinary tract infections

- No ability to stop anticoagulant or antiplatelet therapy

- Medical history of a (potential) bleeding disorder

- Major concurrent debilitating illness or American Society of Anaesthesiologists Physical Status Classification System ≥4

- Chemotherapy for prostate cancer

- Androgen deprivation therapy within last 6 months

- Has any medical condition or other circumstances which would significantly decrease the chances of obtaining reliable data, achieving study objectives, or completing the study

- Is incapable of understanding the language in which the information for the patient is given

Figure 5. Flowchart procedure 1: transperineal template mapping biopsy (TTMB) study design; flowchart procedure 2: robot-assisted laparoscopic prostatectomy (RALP) study design. CLE: confocal laser endomicroscopy; OCT: optical coherence tomography.
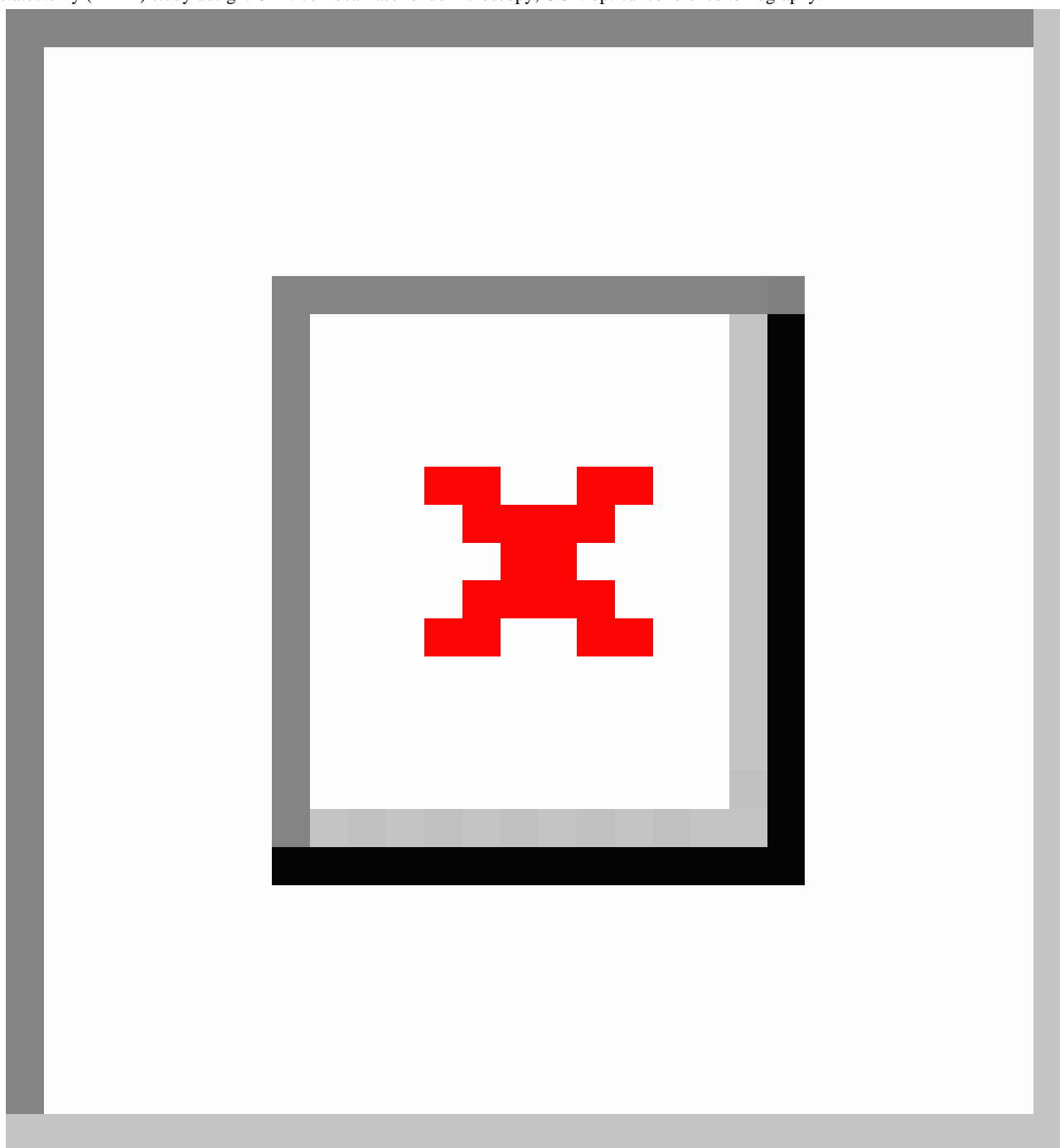
Confocal Laser Endomicroscopy Measurement Technique

For the CLE measurement, 0.5 mL of fluorescein (2.5% fluorescein diluted in saline) is intravenously injected for contrast. The CLE probe is inserted using a 17-gauge trocar needle. When the CLE is in contact with prostate tissue, the measurement begins; while recording, the probe and needle are pushed from apex to base. During this push and scan technique, the probe stays in contact with the tissue.

Optical Coherence Tomography Measurement Technique

The OCT probe is inserted through a 17-gauge trocar needle. The needle is placed at the end of the measurement trajectory. Then, the trocar needle is pulled back, so the probe is in contact with the surrounding tissue. When the probe is in contact, an OCT measurement will be made. The measurement is performed from base to apex.

Procedure 2: Robot-Assisted Laparoscopic Prostatectomy (10 Patients, 5 Confocal Laser Endomicroscopy Imaging and 5 Optical Coherence Tomography Imaging)

In the operating theater, before the RALP, the CLE or OCT measurements will be obtained in the same fashion as in procedure 1. Dimensions of the prostate will be measured on the ultrasound console. Following marked regions from the mpMRI, the CLE or OCT measurements will be made following the technique described earlier. After measurement, a plastic

cannula will be left in the specific trajectory as a localization marker. This marker shows the measurement location necessary for analysis once the prostate has been removed. After the cannula placement, the TRUS-probe and stepper will be removed, and the standard RALP can start. The plastic cannulas will remain in place during the removal of the prostate. Figure 5 shows the flowchart of procedure 2.

Multiparametric Magnetic Resonance Imaging

MpMRI is a combination of T2-weighted MR imaging, diffusion-weighted MR imaging, and dynamic contrast-enhanced MR imaging. MpMRI of the prostate enables detection of the prostate tumor with reasonable sensitivity and specificity values [33]. MpMRI will be evaluated by a uroradiologist for evidence of PCa localization according to the PI-RADSv2 criteria [34].

Data Analysis

Demographic and disease-specific characteristics of the study populations (eg, age, PSA, DRE, biopsy localization, tumor location on imaging and pathology, tumor size, and Gleason score) will be collected. First, CLE and OCT data will be evaluated in a qualitative way. The data will be compared with histopathology, and characteristics of the following different tissues in the prostate will be described; benign glands, cystoid atrophy, regular atrophy, stroma, malignant tissue using the Gleason score, inflammation, and fat. The data will be obtained and analyzed by nonblinded investigators, and subsequently, investigators blinded to the results will interpret all individual measurements for diagnostic evaluation. An independent uropathologist, blinded for the CLE and OCT results will perform the histopathology. Second, OCT data will be analyzed quantitatively. We will determine and report the attenuation coefficient, the decay of light in tissue, per tissue type in the prostate [15,35].

Safety

The investigators will monitor patient safety. They can withdraw a patient from the study for medical reasons. In accordance to section 10, subsection 4, of the "Wet Medisch-Wetenschappelijk Onderzoek met Mensen" (medical research involving human subjects act in the Netherlands), the investigators will suspend the study if there is sufficient ground that the continuation of the study will jeopardize patient's health or safety. The investigators will notify the accredited IRB if this is the case. In case of an adverse event or serious adverse event, the responsible authorities will be informed.

Benefits and Risks

As the patients included in this study are already scheduled for radical prostatectomy or TTMB, no direct benefit exists. The results of this study may be relevant for patients in the future for PCa diagnosis, grading, and staging. CLE and OCT are promising imaging techniques that in conjunction with the TRUS/mpMRI fusion guided biopsy procedure can provide real-time, high-resolution 3D microscopic imaging and tissue characteristics of PCa.

Previous in vivo studies using CLE or OCT did not report any adverse events, and these modalities are performed by needle guidance with the same diameter or smaller as the standard biopsy needles. In case of a RALP, 2 plastic cannulas will be placed using an intravenous needle. The plastic cannulas will stay in the prostate during the surgery and could, therefore, harbor an increased risk for infection, positive surgical margin rate, or other (unknown) complication during surgery. Standard antibiotic prophylaxis (ciprofloxacin) will be administered 2 h before surgery to reduce the risk of infection. The proposed needle-based imaging techniques also imply a puncture into the prostate and, therefore, have a risk of complications such as bleeding. However, bleeding is believed to be limited as only 2 needles will be placed; complications will be documented and critically analyzed in this safety and feasibility study. Fluorescein is a commonly used fluorescent dye that will be administered intravenously through an intravenous cannula. Previous reports have proven that it is safe and easy to administer [36-38]. Possible side effects include nausea, vomiting, abnormal taste sensations, thrombocytopenia, and allergic reactions. Patients with a known allergic reaction to fluorescein are excluded from participation in this study. Standard care and pathological evaluation as stated by the internal protocols will not be affected in this study. In conclusion, we believe that the burden and risk associated with participation in this study are limited.

Results

Presently, recruitment of patients is ongoing in the study. Results and outcomes are expected in 2019. Summarized raw data will be made available through publication in an international peer-reviewed medical journal.

Discussion

This protocol describes the first in vivo study for needle-based optical biopsies using CLE and OCT in the prostate. Both techniques may enable real-time pathological information by showing cellular characteristics on CLE images and microarchitecture on OCT images. The study comprises 2 parts: feasibility of the technology and comparison with histology.

This first part contains multiple similarities with the protocol of Wagstaff et al using needle-based OCT in the kidney [16]. Using ultrasound guidance, a trocar needle was placed to guide the OCT needle and subsequently the standard biopsy needle, both sampling the same location. Instead of using a trocar needle, in this protocol, a transperineal grid will be used as a guidance tool. This transperineal grid will allow targeting of the suspected lesion based on cognitive fusion with prostate mpMRI, which has shown to be as good as automatic fusion [39]. The expected burden for the patients is thought to be minimal by using only 2 extra needles; by target placement of the 2 needles, the possibility of sampling the lesion is as high as possible.

The second part of the protocol enables one-to-one comparison of in vivo data with histology for both CLE and OCT. Our approach is similar to the approach of Muller et al [28] that compared ex vivo needle-based OCT measurements of radical prostatectomy specimens with histology by cutting through the measurement trajectories. In our measurements, data will be

obtained from in vivo tissue, in which red blood cells will absorb and scatter light different from regular cells. Due to the perfusion of prostate tissue, the acquired data will most probably differ from the ex vivo measurements [29,40]. Nonetheless, this study will enable us to understand the in vivo OCT and CLE images and challenges in co-localization of acquired in vivo data with ex vivo histology.

In the described study, safety and feasibility of both imaging techniques are assessed in patients under operating theater circumstances with general or spinal anesthesia. Although safety and feasibility could be different in patients under local anesthesia in an outpatient setting, we expect that both proposed needle-based imaging techniques are easily translated to an outpatient setting as both use equal or smaller diameters as biopsy guns and both are designed to be integrated into the outpatient workflow.

Several studies have provided in vivo images of CLE, but do not show a comparison with histology or an in-depth interpretation of the prostate images [38]. On the basis of histopathology, it is expected that benign prostate tissue differs in extracellular structure compared with malignant prostate tissue. The fluorescein, provided by intravenous injection, gives contrast to the extracellular matrix on the CLE images, which could potentially allow to discriminate between benign and malignant prostate tissue. The described protocol will compare histology and CLE to provide knowledge of visual characteristics on CLE images.

Locating and recording the position of the in vivo measurements is difficult and will be less precise than an ex vivo measuring environment. The in vivo measurement locations will be mapped by ultrasound, and the measurement trajectory will be marked for ex vivo histology comparison. Regardless of this precise measurement mapping, the size and shape of the prostate will change after removal and formaldehyde fixation and could cause potential correlation errors [41]. These changes in dimensions will be recorded by measuring the size of the in vivo prostate by ultrasound and when fixated, to be able to correct for prostate shrinkage. During the comparison of in vivo measurements and ex vivo histopathology, the measurement trajectory will be scaled. The length of the measurement trajectory will be scaled following the shrinkage of the prostate. Shrinkage of tissue over the trajectory is not uniform, but this is in our opinion is the best available option to correct for the shrinkage.

This study is an essential first step for the clinical evaluation of optical imaging in PCa diagnosis. In the clinic, a tool for optical histology could potentially guide a biopsy needle with instant feedback of the region of interest for reliable diagnosis and treatment of PCa.

Authors' Contributions

AS, MJVS, DMdB, and JJMCHdlR conceived the trial concept. AS, CKM, MJVS, JAN, and DMdB designed the protocol for IRB approval. AS and CKM organized the trial logistics. AS, CSH, TGvL, and DMdB facilitate imaging analysis. AS, CKM, RJAvM, and TMdR oversee the interpretation of this study. AS and CKM drafted the manuscript. All authors reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CLE: confocal laser endomicroscopy
IRB: institutional review board
mpMRI: multiparametric magnetic resonance imaging
OCT: optical coherence tomography
PCa: prostate cancer
PI-RADS: prostate imaging reporting and data system
PSA: prostate-specific antigen
RALP: robot-assisted laparoscopic prostatectomy
TRUS: transrectal ultrasound
TTMB: transperineal template mapping biopsy

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Protocol

Applicability of a Web-Based, Individualized Exercise Intervention in Patients With Liver Disease, Cystic Fibrosis, Esophageal Cancer, and Psychiatric Disorders: Process Evaluation of 4 Ongoing Clinical Trials

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Abstract

Background: In the primary and secondary prevention of civilization diseases, regular physical activity is recommended in international guidelines to improve disease-related symptoms, delay the progression of the disease, or to enhance postoperative outcomes. In the preoperative context, there has been a paradigm shift in favor of using preconditioning concepts before surgery. Web-based interventions seem an innovative and effective tool for delivering general information, individualized exercise recommendations, and peer support.

Objective: Our first objective was to assess feasibility of our Web-based interventional concept and analyze similarities and differences in a sustained exercise implementation in different diseases. The second objective was to investigate the overall participants' satisfaction with our Web-based concept.

Methods: A total of 4 clinical trials are still being carried out, including patients with esophageal carcinoma scheduled for oncologic esophagectomy (internet-based perioperative exercise program, iPEP, study), nonalcoholic fatty liver disease (hepatic inflammation and physical performance in patients with nonalcoholic steatohepatitis, HELP, study), depression (exercise for depression, EXDEP, study), and cystic fibrosis (cystic fibrosis online mentoring for microbiome, exercise, and diet, COMMED, study). During the intervention period, the study population had access to the website with disease-specific content and a disease-specific discussion forum. All participants received weekly, individual tailored exercise recommendations from the sports therapist. The main outcome was the using behavior, which was obtained by investigating the log-in rate and duration.

Results: A total of 20 participants (5 from each trial) were analyzed. During the intervention period, a regular contact and a consequent implementation of exercise prescription were easily achieved in all substudies. Across the 4 substudies, there was a significant decrease in log-in rates ($P<.001$) and log-in durations ($P<.001$) over time. A detailed view of the different studies shows a significant decrease in log-in rates and log-in durations in the HELP study ($P=.004$; $P=.002$) and iPEP study ($P=.02$; $P=.001$), whereas the EXDEP study ($P=.58$; $P=.38$) and COMMED study ($P=.87$; $P=.56$) showed no significant change over the 8-week intervention period. There was no significant change in physical activity within all studies ($P=.31$). Only in the HELP study, the physical activity level increased steadily over the period analyzed ($P=.045$). Overall, 17 participants (85%, 17/20) felt secure and were not scared of injury, with no major differences in the subtrials.

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Conclusions: The universal use of the Web-based intervention appears to be applicable across the heterogonous collectives of our study patients with regard to age and disease. Although the development of physical activity shows only moderate improvements, flexible communication and tailored support could be easily integrated into patients' daily routine.

Trial Registration: iPEP study: ClinicalTrials.gov NCT02478996; https://clinicaltrials.gov/ct2/show/NCT02478996 (Archived by WebCite at http://www.webcitation.org/6zL1UmHaW); HELP study: ClinicalTrials.gov NCT02526732; http://www.webcitation.org/6zJjX7d6K (Archived by WebCite at http://www.webcitation.org/6Nch4ldcL); EXDEP study: ClinicalTrials.gov NCT02874833; https://clinicaltrials.gov/ct2/show/NCT02874833 (Archived by WebCite at http://www.webcitation.org/6zJjj7FuA)

Introduction

There is a worldwide trend toward higher incidence of Barrett cancer [1-3], depression [4], or nonalcoholic fatty liver disease (NAFLD) [5-7], and an alarming increase in overweight and obesity [8]. Being physically active reduces not only the risk for numerous diseases [9] but also stabilizes or slows down disease progression [10-13]. However, chronic conditions require continuous exercise [10,11]. Currently, regular physical activity is recommended in treating chronic diseases according to more elaborated, modern investigations [14,15]. Despite this fact, many patients are unable to perform moderate exercise in the long term [16], mainly due to numerous obstacles in initiating and maintaining an active lifestyle [17]. For instance, studies showed a reduced physical activity level (intensity and amount) in patients with NAFLD compared with healthy controls [18-24]. Changing lifestyle is not easy, especially for this group of patients with sedentary habits [25]. Consequently, regular motivational support from experts to achieve lifestyle changes is recommended [25]. Supervised face-to-face programs with an expert seem also to improve compliance regardless of the type of disease [16,26,27]. However, exercise intensity, duration, and frequency need to be planned carefully for the purpose of enhancing physical health [9]. To provide close support in the long term and in a sustainable manner, which is focused on the flexibility of the patient, the internet seems to be a suitable tool. It has been shown that novel Web-based interventions might be a cost-effective, complementary alternative for a close supervision despite the distance to the real treatment location [28-30]. Outstanding advantages of Web-based interventions are as follows: an easy access regardless of place and time and the anonymous nature [3,29-38]. Therefore, and based on the promising results of previous trials [39-41], we decided to support patients with different diseases (esophageal [Barrett] carcinoma, NAFLD, depression, and cystic fibrosis) with a Web-based, individualized, supervised concept. The common platform for all these patient groups is a key aspect in our concept. We focused on regular feedback and recommended adjusted activity goals instead of self-chosen targets, to improve the fitness as well as disease-specific conditions. In this study, we focus predominantly on the various methodological challenges [42]. Therefore, the following 3 questions will be addressed:

1. Is our Web-based intervention concept feasible in different disorders (assessed by evaluating the log-in rate and log-in duration)?
2. What are the similarities and differences between the diseases in terms of exercise implementation (assessed by evaluating the training time and interruptions)?
3. Are the study participants satisfied with the Web-based concept (assessed by Likert items)?
   Our results may provide planning support for future investigations and study designs.

Methods

Design

The webpage went online in 2015. This study consists of 4 substudies that are still ongoing and had separately been approved by the ethics committees. Eligible patients were recruited and screened in 6 University Medical Centers, and all patients provide signed informed consent. In Figure 1, the 4 clinical trials are described.

Due to the diseases studies being different, the primary outcomes and the inclusion and exclusion criteria vary between the substudies. In Table 1 the primary and secondary outcomes of the substudies are summarized. The HELP study (hepatic inflammation and physical performance in patients with nonalcoholic steatohepatitis [NASH]) and the COMMED study (cystic fibrosis online mentoring for microbiome, exercise, and diet) are prospective single-arm trials. The EXDEP study (exercise in depression) and the multicenter iPEP study (internet-based perioperative exercise program) are randomized controlled trials. Patients in the control groups had no access to the webpage (treatment as usual).

Data of patients in the iPEP study were collected at 3 time points. Baseline (t0) was at diagnosis (8-12 weeks before surgery, depending on the date of surgery). The first follow up (t1) was immediately before surgery to show the impact of the exercise program. The final examination (t2) was performed 12 weeks post surgery. In the EXDEP study and HELP study, the patients were tested at study start (t0) and 8 weeks later (t1). In the COMMED study, the study participants were compared with 3 points in time: to study start (t0), 12 weeks later (t1), and after 12 months (t2).

Figure 1. The applied Web-based exercise support concept. HELP: hepatic inflammation and physical performance in patients with NASH; iPEP: internet-based perioperative exercise program; COMMED: cystic fibrosis online mentoring for microbiome, exercise, and diet; EXDEP: exercise for depression.
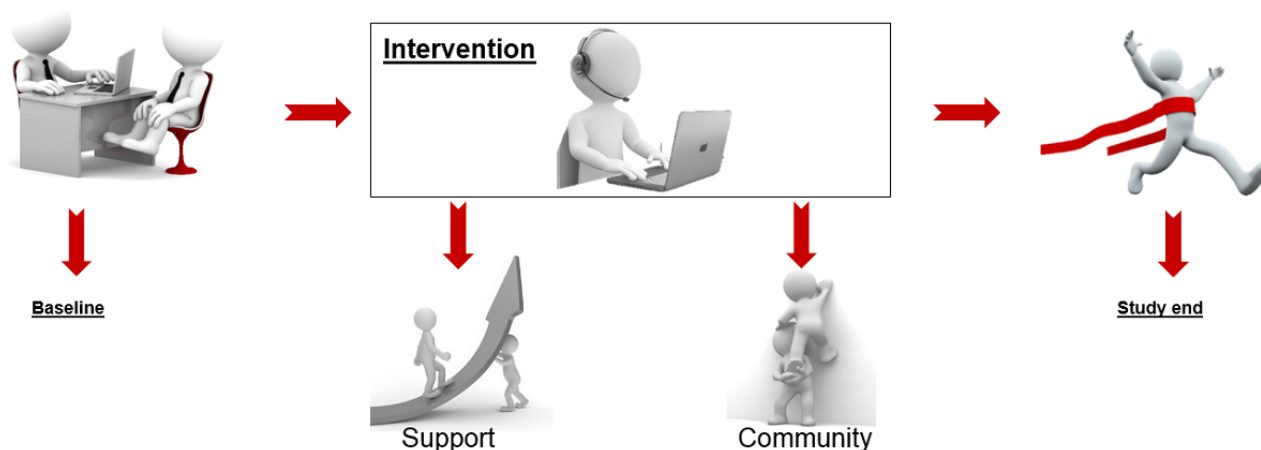
	Intervention period	Special features	Already recruited
iPEP study	10-12 weeks prior surgery & 10-12 weeks after surgery	Biweekly live chat	n=22 (of 80)
HELP study	8 weeks	Biweekly face-to-face training	n=44 (of 46)
EXDEP study	8 weeks	Biweekly face-to-face training	n=20 (of 20)
COMMED study	1 year	During routine hospitalization one-to-one training	n=15 (of 20)

Table 1. The primary and secondary outcomes of the 4 clinical trials.

Study	Primary objective	Secondary objective
iPEP[a]	Change of peak oxygen uptake (VO_{2peak})	Gastric conduit failure after esophagectomy; evaluation of postoperative in-hospital stay; quality of life questionnaire QoLQ-C30 with the esophagus-specific module Oesophageal-18
HELP[b]	Change of VO_{2peak}	Change of NAS[c] score at week 0 and week 8
EXDEP[d]	Change of score on the Quick Inventory of Depressive Symptomatology clinician version 16 after 8 weeks compared with baseline; change of score on the Quick Inventory of Depressive Symptomatology self-report version 16 after 8 weeks compared with baseline.	Change of VO_{2peak} after 8 weeks compared with baseline; change of score on the short form-36 after 8 weeks compared with baseline.
COMMED[e]	Changes of fecal and respiratory microbiome, fecal calprotectin, tumor necrosis factor alpha, and VO_{2peak}	Changes of FEV1[f]; change of forced vital capacity; change of quality of life

[a]iPEP: internet-based perioperative exercise program.

[b]HELP: hepatic inflammation and physical performance in patients with NASH.

[c]NAS: NAFLD activity score.

[d]EXDEP: exercise for depression.

[e]COMMED: cystic fibrosis online mentoring for microbiome, exercise, and diet.

[f]FEV1: forced expiratory volume in 1 second.

The inclusion criteria in the iPEP study were (1) histologically proven adenocarcinoma of the esophagus or adenocarcinoma of the esophagogastric junction type I according to Siewert's classification, clinical stages IIB-IIIC (T3/T4 and/or N+; M0) according to Union Internationale Contre le Cancer, 7th Edition; (2) resectable stage according to discussion in the local multidisciplinary tumor board of the participating centers and patient medically fit for multimodality therapy (Eastern Cooperative Oncology Group performance status at least 1 or better, no severe impairment of cardiac, renal, hepatic, endocrine, bone marrow, and cerebral functions); (3) planned abdominal-thoracic esophagectomy with gastric pull-up and intrathoracic or cervical anastomosis; and (4) cognitive ability of the patient to understand the perioperative program and to participate actively.

The exclusion criteria were (1) the presence of a second malignant tumor (unless curatively treated >5 years ago); (2) chemotherapy or radiochemotherapy in patient's history; (3) orthopedic, rheumatologic, cardiovascular, or neurologic

(epilepsy, stroke, Parkinson disease, muscle wasting diseases such as amyotrophic lateral sclerosis or multiple sclerosis) contraindications for the sports program; (4) inability to use the internet or no internet access; (5) inability to communicate in German; (6) each active disease that hinders completion of the study; and (7) active alcoholism or illegal drug consumption within the last 6 months before study entry.

The inclusion criteria for the HELP study were (1) histologically proven NASH or fatty liver disease.

The exclusion criteria were (1) bariatric surgery within the last 5 years, (2) body mass index (BMI) <18.5 kg/m^2 or >45 kg/m^2, (3) heart attack or stroke within the last 6 months, (4) higher grade coronary artery disease (CADIII-IV), (5) chronic obstructive pulmonary disease (asthma, COPD), (6) renal insufficiency, (7) uncontrolled hypertension or metabolic abnormalities, (8) alcohol consumption >30 g/day (male) and >20 g/day (female), (9) pregnancy, (10) concomitant medication able to cause a secondary NASH (eg, tamoxifen, corticosteroids), (11) concomitant medication able to affect inflammation (eg, tumor necrosis factor antagonists), (12) concomitant anticoagulant medication (eg, phenprocoumon; novel oral anticoagulants, NOAC), (13) other immunological or inflammatory diseases (eg, systemic lupus erythematosus), and (14) musculoskeletal disorders, preventing sport physiological investigations.

The inclusion criteria for the EXDEP study were (1) ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations; (2) aged 18 to 65 years, inclusive, at the time of informed consent; (3) Montreal Cognitive Assessment >26 to exclude cognitive impairment; (4) apart from a clinical diagnosis of major depression or bipolar affective disorder, the subject must be in good health as determined by the Investigator, based on medical history and physical examination; (5) Quick Inventory of Depressive Symptomatology scores >5.

The exclusion criteria were (1) use of antidepressive medications or benzodiazepines at doses that have not been stable for at least 6 weeks before screening; (2) psychotherapy that started less than 8 weeks before screening; (3) any clinically significant psychiatric illness other than major depression or bipolar affective disorder; (4) transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year before screening; (5) any uncontrolled medical or neurological/neurodegenerative condition that, in the opinion of the investigator, might impair treatment compliance and adherence; (6) history of unstable angina, myocardial infarction, chronic heart failure (New York Heart Association Class III or IV), or clinically significant conduction abnormalities (eg, unstable atrial fibrillation) within 1 year before screening; (7) clinically significant 12-lead ECG abnormalities, as determined by the investigator; (8) uncontrolled hypertension defined as: average of 3 systolic blood pressure/diastolic blood pressure readings >65/100 mmHg at screening; (9) history of malignancy or carcinoma, with the following exceptions: (i) subjects with

cancers in remission more than 5 years before screening, (ii) subjects with a history of excised or treated basal cell or squamous carcinoma, (iii) subjects with prostate cancer in situ; (10) history of seizure within 2 years before screening; (11) recent history (within 1 year of screening) of alcohol or substance abuse as determined by the investigator, a positive urine drug (due to nonprescription drug) or alcohol test at screening; (12) clinically significant systemic illness or serious infection (eg, pneumonia, septicemia) within 30 days before or during screening; (13) history of HIV, hepatitis C virus, or hepatitis B virus; (14) any other medical conditions (eg, renal disease) that are not stable or controlled, or, which in the opinion of the investigator, could affect the subject's safety or interfere with the study assessments; (15) female subjects who are pregnant or currently breastfeeding; (16) participation in another study; (17) other unspecified reasons that, in the opinion of the investigator or Biogen, make the subject unsuitable for enrollment.

The inclusion criteria for the COMMED study were (1) age >12 years (2) forced expiratory volume in 1 second (FEV1) <90% and >28% of the set point or FEV1 >90% or/and lung clearance index LCI >9.

The exclusion criteria were (1) orthopedic, rheumatologic, cardiovascular, or neurologic contraindications for the sports program; (2) inability to use the internet or no internet access; (3) inability to communicate in German; (4) the absence of consent; (5) further cystic fibrosis–specific criteria: (i) severe pulmonary exacerbation, (ii) FEV1 <27% of the set point (standard value Global Lung Initiative), and (iii) acute infection.

Cardiopulmonary Exercise Test

Before the start of the study, all eligible study participants performed a stepwise cardiopulmonary exercise test until volitional exhaustion. Each stage of the modified walking protocol lasted for 3 min and intensity was increased by speed and elevation of the treadmill. During the test, heart rate (HR) and respiratory gas analysis were continuously monitored. Furthermore, blood samples from the earlobe were taken at the end of each stage to determine lactate concentration. Subjective degree of exhaustion was measured utilizing the Borg scale (6-20) 30 s before the end of each stage [43].

Intervention Design

For study design and content structure of the website, experiences from other studies were considered [29,44-46]. Similar to Barak et al (2009), we took the key components of a Web-based intervention into account. We delivered program content, used multimedia aspects, promoted interactive Web-based activities, and provided tailored feedback [37]. Participants were registered on the home page by the administrator and a printed (also online available) instruction manual was provided. Once registered and logged in, users were able to change their profile by editing or deleting information such as username, profile picture, or password. Relevant aspects of data protection were taken into account. The various disease intervention groups obtained access to different parts of the website (Figure 2).

Figure 2. The home screen of the webpage with the divided disease-specific classrooms.
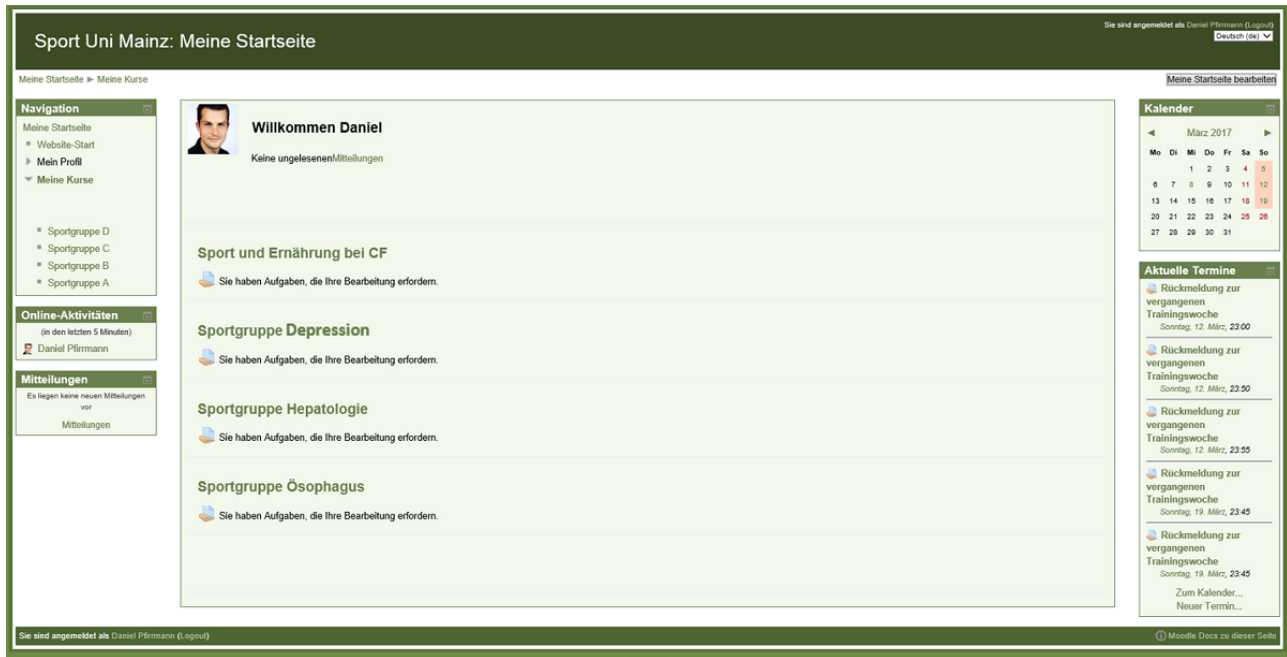
Besides the interaction with a counselor, peer support was considered as a basic principle of our concept. Therefore, each subgroup had its own discussion forum and chat room to improve social support and adherence [46]. Furthermore, nutritional experts or supervising physicians distributed quickly and easily the disease-specific questionnaires and informative documents.

Exercise Support

To improve the current condition, sport scientists were responsible for training management and weekly recommendations. Individually tailored exercise plans were sent weekly by an internal email in the secure area of the website. The program consisted of walking or running recommendations, muscle strengthening and stretching exercises, as well as relaxation exercises. An HR monitor (Polar, FT1) was provided to the study participants to monitor the endurance training. The resistance training was carried out in a home-based environment with body-weight exercises and with elastic resistance bands (in different strengths; Pinofit; Pharmazeutische Präparate GmbH, Hamburg) and lasted for approximately 45 min. In addition to an illustrated tutorial, all exercises were additionally deposited as a video file on the home page and could be downloaded or viewed online (Figure 3).

Participants were encouraged to provide training-related information (eg, average HR, duration, subjective perceived exertion) to the supervisor at the end of each week while filling out a schedule. This information helped the trainers to adapt the training load for the upcoming weeks. Due to the individual feedback of study participants, tailored recommendations focused on the needs, problems, and limitations of each participant were possible. Strength and endurance training were examined separately and allowed specific increase or decrease of training content in terms of duration and/or intensity (Figure 4).

Due to a steady contact with the patients, a missing schedule was noticed quickly by the supervisor sending an email to identify possible problems with the program. Patients were able to contact the trainer at any time by an internal email. In case of questions and feedback, the supervisor answered within 24 hours.

Measures

The data on using behavior were assessed by evaluating the log-in rate and log-in duration during the intervention period of 8 weeks. The exercise implementation was assessed by evaluating the training time, exercise interruptions, self-chosen alternative exercise programs instead of the weekly recommendations, and adverse events. The user satisfaction with the exercise concept and the webpage was assessed based on a short questionnaire (8 Likert items). Furthermore, the participants graded the concept and were asked if they would continue to use the webpage.

Analysis

Preliminary descriptive statistics were used to present data on the baseline characteristics of each single trial. Descriptive statistics were also used to show data on utilization and satisfaction with the Web-based exercise concept, as well as exercise adherence and training interruptions and log-in rate and log-in behavior. No data on exercise effects will be presented, due to the heterogeneity of primary outcomes, study collectives, and study designs. Statistical analysis was performed using SPSS (version 22.0, Chicago, IL, USA) and P values $<.05$ were considered significant. Data were not normally distributed and showed heterogeneous variances. Therefore, nonparametric Kruskal-Wallis H-tests were carried out to examine trends of physical activity over time among the substudies. The Dunn-Bonferroni test was additionally used as post hoc test to further determine, where exactly the differences between the groups or time points were located.

Figure 3. The support area of the home page.
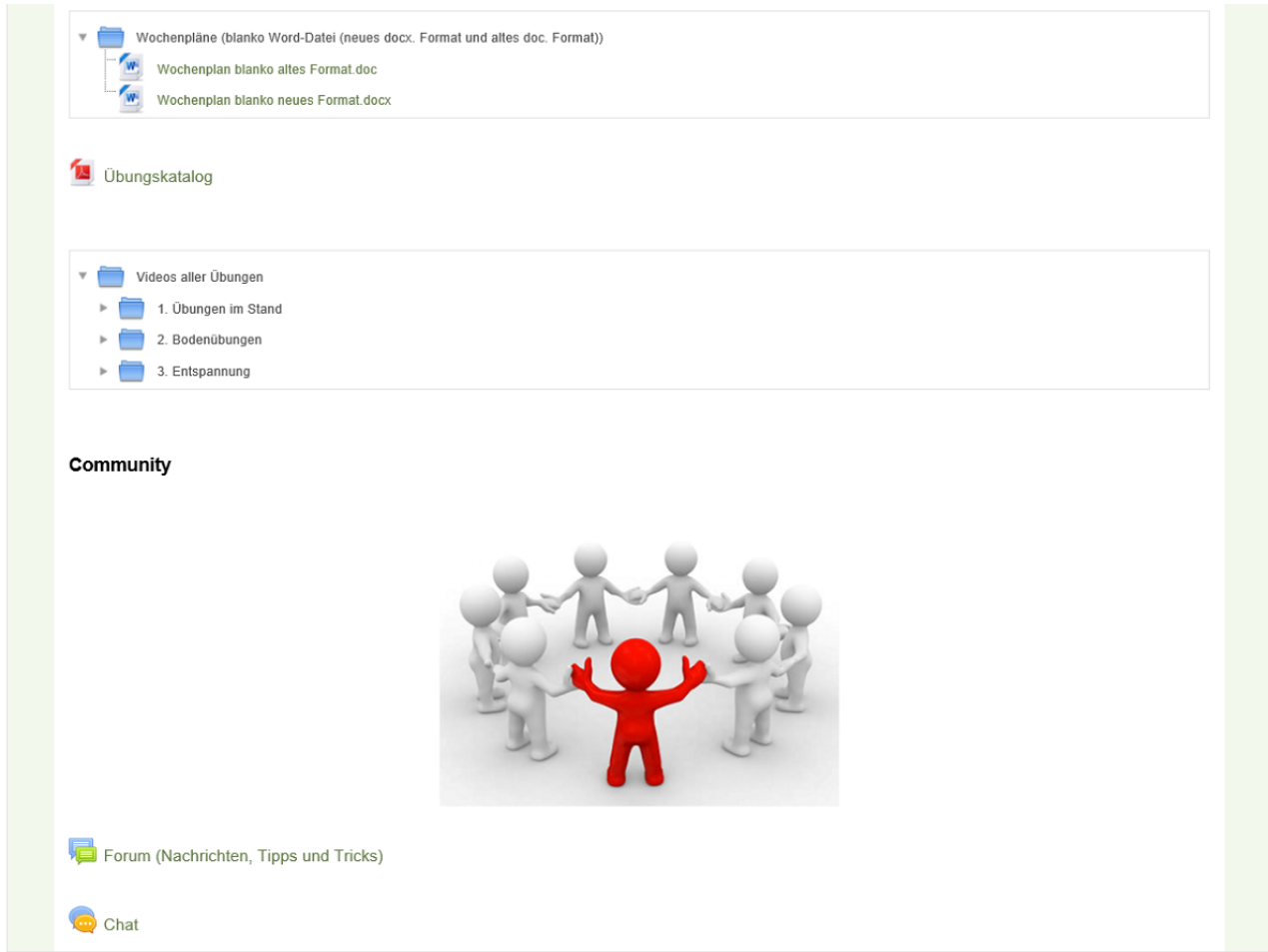
Figure 4. The weekly exercise recommendation structure. Endurance training and strength training were assessed separately.
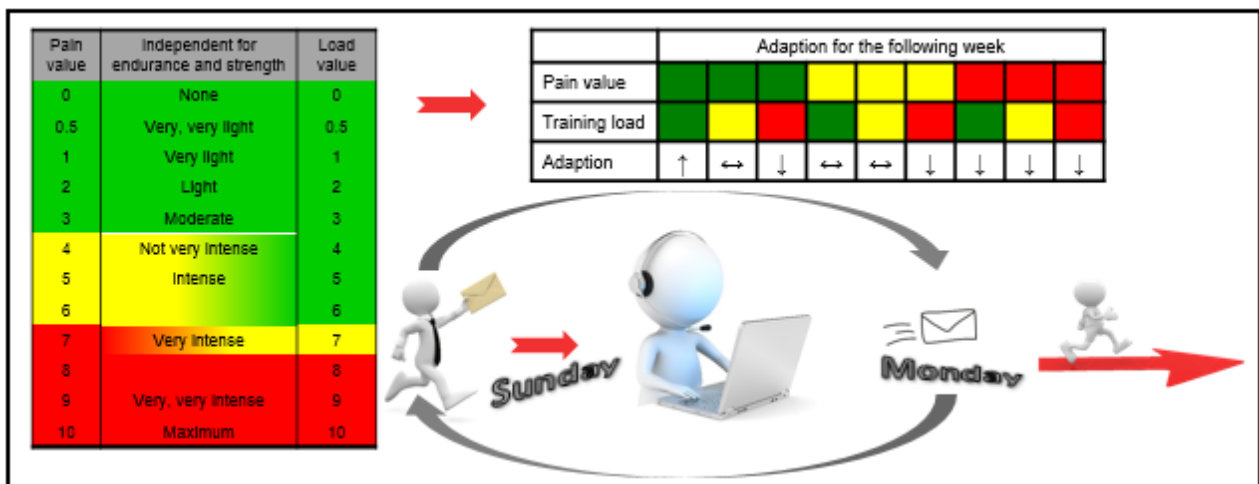
Results

Summary

All study participants were recruited by physicians in the cooperating centers. Due to different recruiting processes of the single trials and different intervention periods, with regard to the present analysis, we present the first 5 recruited study participants of each study over an 8-week period. As summarized in Table 2, characteristics of the 20 study participants and primary outcome measures at baseline are presented. The patient flow of each trial is shown in Figure 5.

Participants' Characteristics

In Table 2, the main baseline characteristics are summarized. The majority of participants were males (n=12) and showed similar distributions with respect to cardiorespiratory fitness. Mean age was 42 years (SD 14.54 years), and mean BMI was 26 kg/m^2 (SD 3.91 kg/m^2). Patients in the HELP study tended

to be obese (BMI: 30 kg/m^2; SD: 3.02 kg/m^2), whereas patients in the COMMED study tended to be underweight (BMI: 22 kg/m^2; SD: 1.42 kg/m^2). There was a difference in age across all groups. Patients of the COMMED study were younger (32 years; SD: 7.91 years) due to the congenital disease, whereas Barrett cancer patients in the iPEP study were older (55 years; SD: 5.45 years; $P<.001$). Additionally, there was a significant difference in body weight ($P<.001$) and BMI ($P<.001$) between patients of the COMMED and HELP study. However, a low cardiorespiratory fitness level was common in all substudies compared with sex-specific normative data according to the Heywood classification [47] and the comprehensive investigation by Herdy et al [48].

Patients' Acceptance of the Web-Based Concept

Are Web-Based Interventions Feasible in Different Disorders?

During the intervention period, a regular contact (at least once a week) and a consequent implementation of exercise prescription were easily achieved in all substudies. The registration process and the detailed explanation took about 1 hour and could be simply integrated in the physical examination at the study start. During the intervention period, there were on average 17 (SD 8.50) log-ins registered across all studies (Table 3). On average, the study participants stayed within 1 log-in for 14 min on the home page. A total of 8 patients (of 20) checked the webpage less than 2 times a week, and 7 (of 20) stayed on average less than 10 min with each stay. Nevertheless, there

was a decrease in log-in rates and log-in durations with time. The development of the website utilization is presented in Figures 6 and 7. However, regular communication and the weekly return of the exercise feedback were still realized by email and phone (messenger app) contact.

A detailed view of the different studies shows that all patients of the COMMED study checked the webpage less than 2 times a week and stayed there less than 9 min, whereas the group of the EXDEP study logged-in 2.6 times a week into the webpage and was online for more than 23 min with each stay (Table 3).

During the intervention period, there was a decrease in log-in rates and log-in durations in the HELP study and in the iPEP study, whereas the EXDEP study and COMMED study showed no noteworthy change in the log-in rates and the log-in duration patterns over the 8 weeks of the intervention period. However, there was a higher level in log-in rates and log-in durations in the EXDEP study compared with the COMMED study (Figures 8 and 9). To provide maximum flexibility, the patients were able to contact the study team also by an email or a mobile phone. Of all participants in HELP study, 1 participant called the sports therapist 3 times during the intervention period and sent 3 of the 8 exercise schedules per email. As shown in Figure 8, there is a general lower usage activity in COMMED participants. Of all 5 patients, 3 patients used email contact instead of the webpage for communication with the study team. In total, there were 24 messages sent per email. In the EXDEP study and iPEP study, the communication was realized through the webpage only.

Table 2. Baseline patients' characteristics, demographic data and initial cardiorespiratory results.

Baseline characteristics	iPEP[a] (N=5)	HELP[b] (N=5)	EXDEP[c] (N=5)	COMMED[d] (N=5)	Total (N=20)
Age, years (SD)	55.2 (5.45)	34.8 (11.38)	49.0 (16.32)	32.4 (7.91)	42.85 (14.54)
Age groups, n (%)					
<30 years	0 (0)	2 (40)	1 (20)	2 (40)	5 (25)
30-60 years	4 (80)	3 (60)	2 (40)	3 (60)	12 (60)
>60 years	1 (20)	0 (0)	2 (40)	0 (0)	3 (15)
Women, n (%)	0 (0)	2 (40)	3 (60)	3 (60)	8 (40)
Height, cm (SD)	179.40 (5.96)	174 (12.02)	170.80 (8.39)	169.80 (11.80)	173.50 (10.47)
Weight, kg (SD)	84.6 (6.0)	92.8 (22.7)	75.5 (14.4)	64.8 (7.9)	79.4 (17.0)
BMI[e], kg/m^2 (SD)	26.34 (2.36)	30.2 (3.02)	25.84 (3.83)	22.44 (1.42)	26.22 (3.91)
Spiroergometry					
HR[f] max, bpm (SD)	168 (5.19)	177 (5.47)	162 (23.85)	173 (9.10)	170 (14.26)
Watt max, W (SD)	132.20 (44.82)	135.20 (44.27)	107.80 (32.01)	108.00 (44.83)	120.80 (42.47)
VO$_{2peak}$, mL/kg/min (SD)	24.28 (4.37)	28.00 (4.07)	26.88 (8.84)	29.52 (5.02)	27.17 (6.15)
Borg rating (range 6-20) scale (SD)	17.8 (1.97)	18.6 (1.37)	18.2 (1.62)	17.8 (1.18)	18.1 (1.58)

[a]iPEP: internet-based perioperative exercise program.

[b]HELP: hepatic inflammation and physical performance in patients with NASH.

[c]EXDEP: exercise for depression.

[d]COMMED: cystic fibrosis online mentoring for microbiome, exercise, and diet.

[e]BMI: body mass index.

[f]HR: heart rate.

XSL·FO

RenderX

Figure 5. The flowchart of patients' recruitment. HELP: hepatic inflammation and physical performance in patients with NASH; iPEP: internet-based perioperative exercise program; COMMED: cystic fibrosis online mentoring for microbiome, exercise, and diet; EXDEP: exercise for depression.
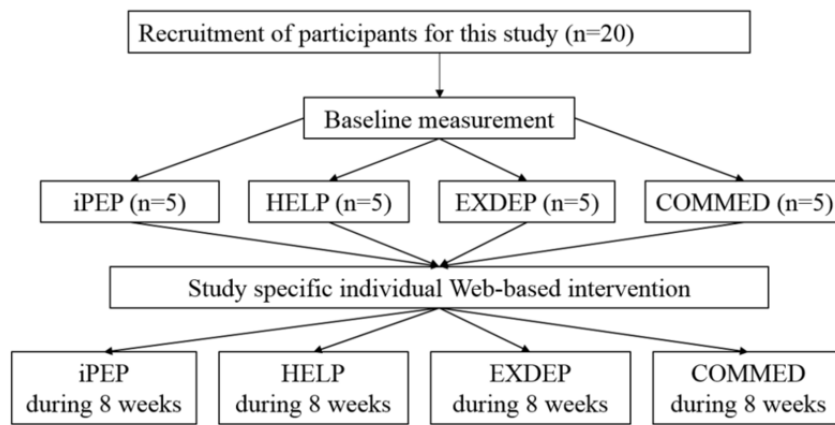
Table 3. Home page usage, log-in frequency, and duration in minutes.

Parameter/variable	iPEP[a] (N=5)	HELP[b] (N=5)	EXDEP[c] (N=5)	COMMED[d] (N=5)	Total (N=20)
Mean number of log-ins (SD)	21.40 (8.02)	15.20 (6.45)	21.00 (7.71)	11.40 (7.60)	17.25 (8.50)
Average number of log-ins per week (SD)	2.68 (1.00)	1.90 (0.81)	2.63 (0.96)	1.43 (0.95)	2.16 (1.06)
Total duration of log-ins (SD)	173.60 (36.10)	229.20 (111.66)	471.00 (246.07)	121.00 (90.32)	248.70 (195.65)
Average log-in duration (SD)	9.54 (4.16)	17.40 (12.99)	23.41 (13.32)	8.17 (4.38)	14.63 (11.49)

[a]iPEP: internet-based perioperative exercise program.

[b]HELP: hepatic inflammation and physical performance in patients with NASH.

[c]EXDEP: exercise for depression.

[d]COMMED: cystic fibrosis online mentoring for microbiome, exercise, and diet.

Figure 6. The development of total log-in rate during 8 weeks of intervention.
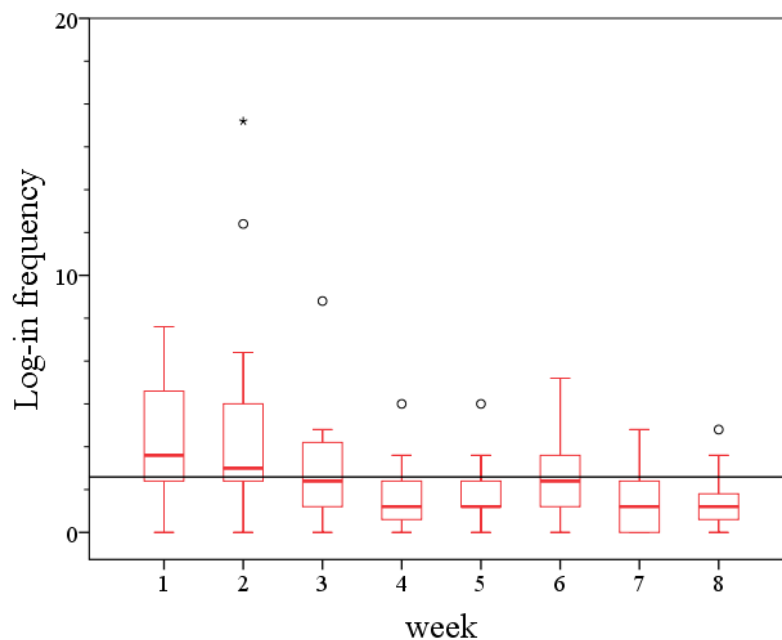
Figure 7. The development of total log-in durations during 8 weeks of intervention.

Figure 8. The development of log-in durations during 8 weeks of the intervention for each study. HELP: hepatic inflammation and physical performance in patients with NASH; iPEP: internet-based perioperative exercise program; COMMED: cystic fibrosis online mentoring for microbiome, exercise, and diet; EXDEP: exercise for depression.
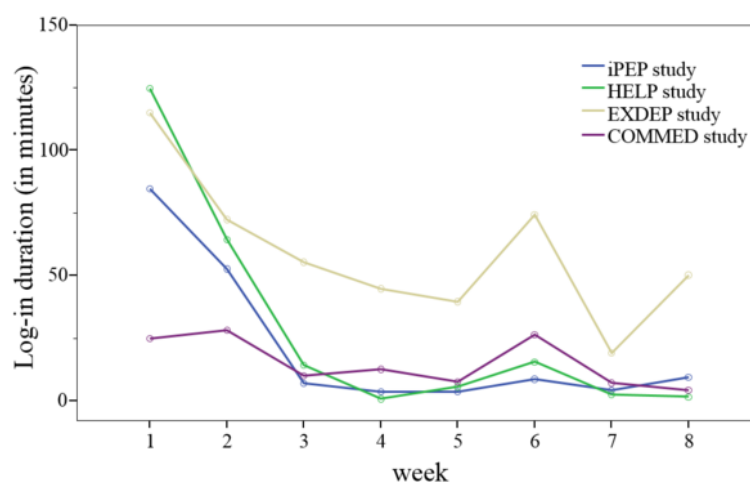
What Are the Similarities and Differences Between the Diseases in Terms of Exercise Sustained Implementation?

The training concept was well-tolerated and accepted by the patients in all trials. No severe adverse events occurred during training; however 8 (of 20) patients expressed minor complaints such as blisters or muscle stiffness at least once during the intervention period. In total, 138 exercise recommendations were not performed, due to different reasons. Common reasons for training interruption were because of working reasons (eg, professional development), medical reasons (eg, cold) external conditions (eg, bad weather), or family reasons (eg, illness in the family). The development of the physical activity level over the first 8 weeks period is shown in Figure 10.

There was no significant change in physical activity within all studies (χ^2_7=8.3, P=.311; Figure 10). Only in the HELP study, the physical activity level increased steadily over the period

analyzed (χ^2_7=14.4, P=.045; Figure 11). Statistically significant differences were observed with respect to total physical activity between the substudies. The participants from both the HELP study (P=.010) and the EXDEP study (P=.001) showed a significant higher activity level compared with the participants of the COMMED study (Figure 12).

However, the development of the physical activity time differed due to different study settings (eg, length of intervention or primary outcome) and the different patient population. Therefore, a comparison of the absolute values between the subgroups was not performed. Especially the 2-phase exercise concept of the iPEP study differed substantially from the other substudies. These patients obtained individual exercise recommendations in the preparation phase for the scheduled surgery. Therefore, an increase in exercise duration was pursued until surgery. However, after surgery and the first weeks of standardized rehabilitation, the exercise concept restarted with reduced advices.

Figure 9. The difference in log-in durations among the substudies. HELP: hepatic inflammation and physical performance in patients with NASH; iPEP: internet-based perioperative exercise program; COMMED: cystic fibrosis online mentoring for microbiome, exercise, and diet; EXDEP: exercise for depression.
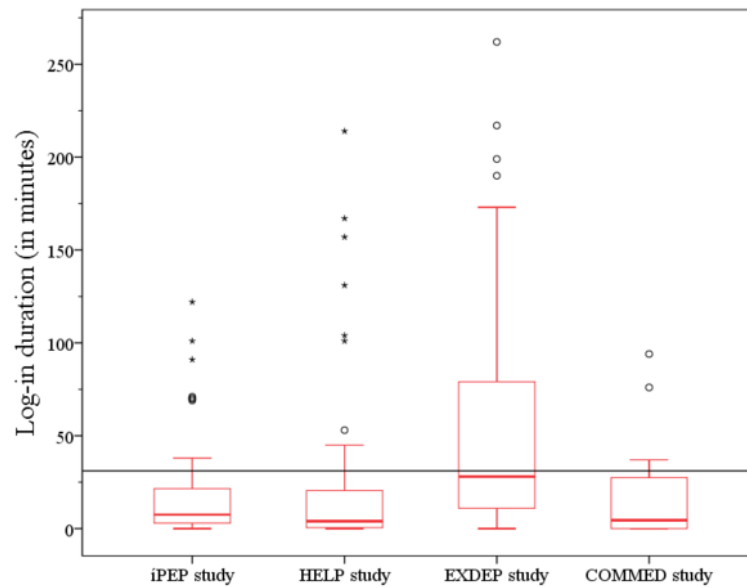
Figure 10. The physical activity development within 8 weeks across all groups.
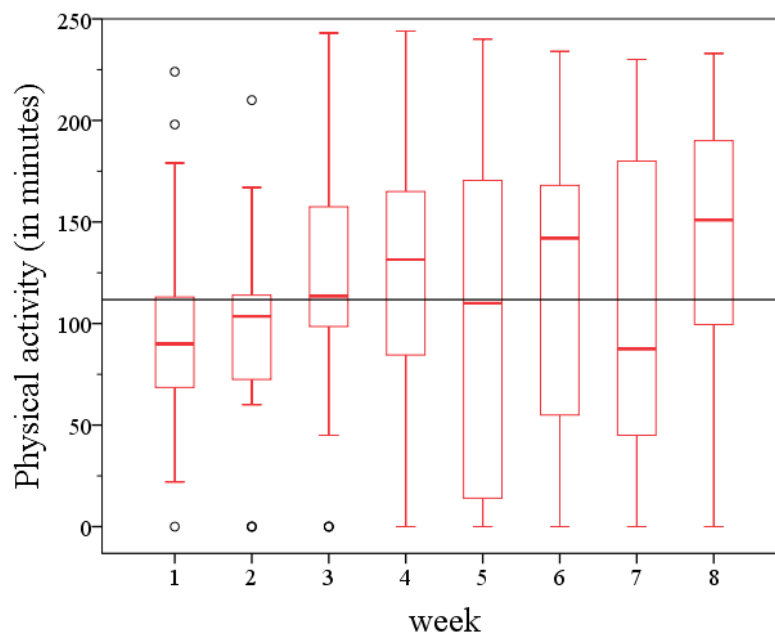
On average, 0.86 (SD 0.75) exercises per week were not performed as instructed (Table 4). We recorded more training interruptions in the COMMED study (mean: 1.13) and the iPEP study (mean: 0.95). Reasons were due to neoadjuvant (radio-/chemo-) therapy in the iPEP cohort and the frequent pulmonary exacerbations of the patients in the COMMED study. Participants in the EXDEP study showed the lowest rate on average with 0.55 interruptions per week. In addition to the recommendations, study participants performed extra workouts or self-chosen alternative exercise programs. In total, 177 alternative sessions were performed. However, 122 of these were completed in the EXDEP study.

Are the Study Participants Satisfied With the Web-Based Concept?

A total of 11 questions had to be answered after study end (Table 5). Participants of all study concepts mentioned no fear of getting injured and felt sufficiently supported. Overall, 85% (17/20) felt secure and were not scared of injury. A total of 9 (of 20) would continue to use the webpage and the exercise concept, and 11 (of 20) gave the intervention a grade between 1 and 2 on a grading scale (ranging from 1=very good to 6=unsatisfactory). There were no major differences in the subtrials. A total of 16 (of 20) participants reported that they felt very personally supported despite the distance.

Figure 11. The physical activity development within 8 weeks in the HELP study. HELP: hepatic inflammation and physical performance in patients with NASH.
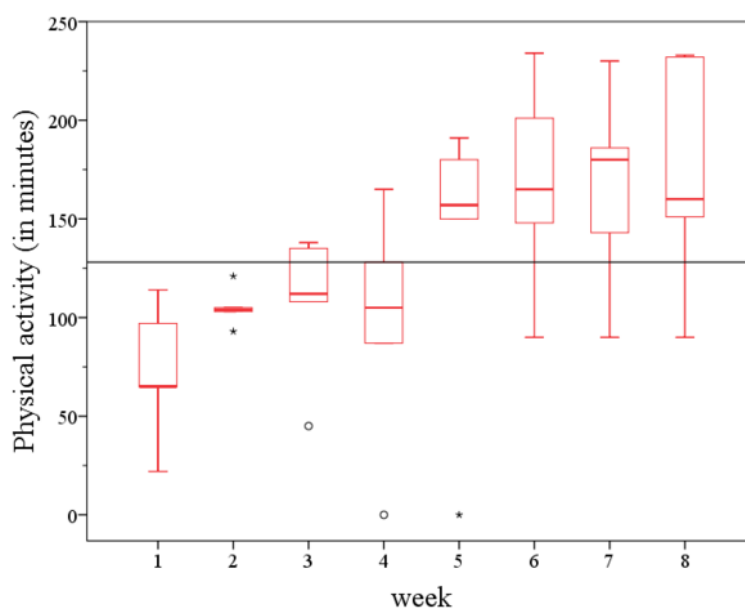
Figure 12. The physical activity level within the 8-week intervention period for each study. HELP: hepatic inflammation and physical performance in patients with NASH; iPEP: internet-based perioperative exercise program; COMMED: cystic fibrosis online mentoring for microbiome, exercise, and diet; EXDEP: exercise for depression.
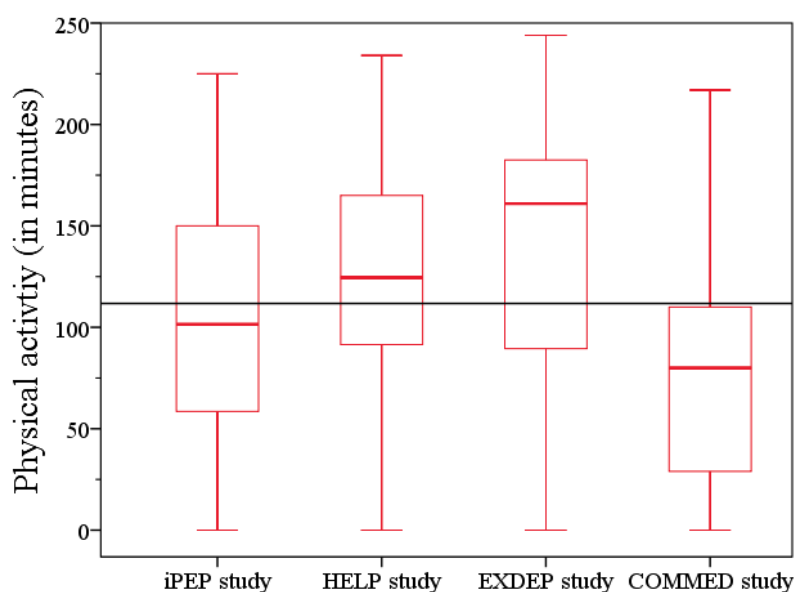
Table 4. Physical activity and training interruption.

Variables	iPEP[a] (N=5)	HELP[b] (N=5)	EXDEP[c] (N=5)	COMMED[d] (N=5)	Total (N=20)
Total physical activity in minutes (SD)	814.20 (286.58)	1024.60 (276.20)	1125.40 (296.22)	639.20 (328.22)	900.85 (349.99)
Average activity per week in minutes (SD)	101.78 (35.82)	128.08 (34.56)	140.68 (37.03)	79.90 (41.03)	112.61 (43.75)
Total training interruption, n (SD)	7.60 (6.42)	6.60 (6.55)	4.40 (3.77)	9.00 (6.04)	6.90 (5.99)
Average number of interruptions per week (SD)	0.95 (0.80)	0.83 (0.82)	0.55 (0.47)	1.13 (0.76)	0.86 (0.75)

[a]iPEP: internet-based perioperative exercise program.

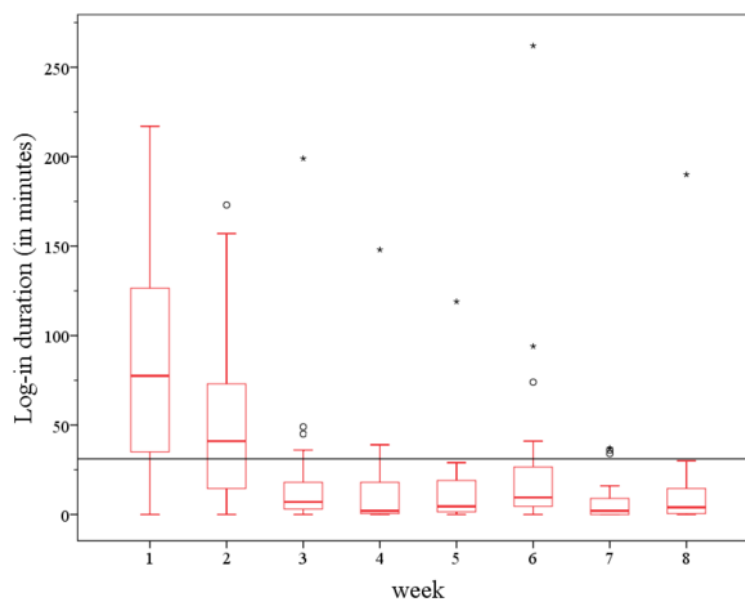[b]HELP: hepatic inflammation and physical performance in patients with NASH.

[c]EXDEP: exercise for depression.

[d]COMMED: cystic fibrosis online mentoring for microbiome, exercise, and diet.

Table 5. Subjective effects and satisfaction.

Question	iPEP[a] (N=5); n (%)	HELP[b] (N=5); n (%)	EXDEP[c] (N=5); n (%)	COMMED[d] (N=5); n (%)	Total (N=20); n (%)
How often did you use the webpage (1-10 scale, 1=not at all, 10=several times a day)					
1	N/A[e]	N/A	N/A	1 (20)	1 (5)
2	2 (40)	1 (20)	2 (40)	N/A	5 (25)
3	N/A	N/A	N/A	N/A	N/A
4	N/A	2 (40)	2 (40)	2 (40)	6 (30)
5	1 (20)	2 (40)	N/A	1 (20)	4 (20)
6	N/A	N/A	N/A	N/A	N/A
7	N/A	N/A	1 (20)	N/A	1 (5)
8	N/A	N/A	N/A	N/A	N/A
9	N/A	N/A	N/A	N/A	N/A
10	N/A	N/A	N/A	N/A	N/A
Not stated	2 (40)	N/A	N/A	1 (20)	3 (15)
How would you rate the training requirements?					
1 Very appropriate	3 (60)	5 (100)	3 (60)	2 (40)	13 (65)
2 Appropriate	N/A	N/A	2 (40)	2 (40)	4 (20)
3 Undecided	N/A	N/A	N/A	1 (20)	1 (5)
4 Inadequate	N/A	N/A	N/A	N/A	N/A
5 Very inadequate	N/A	N/A	N/A	N/A	N/A
6 Not assessable	N/A	N/A	N/A	N/A	N/A
Not stated	2 (40)	N/A	N/A	N/A	2 (10)
How would you rate your fear of injury during training?					
1 No fear at all	3 (60)	5 (100)	4 (80)	5 (100)	17 (85)
2 No fear	N/A	N/A	N/A	N/A	N/A
3 Undecided	N/A	N/A	N/A	N/A	N/A
4 Little fear	N/A	N/A	N/A	N/A	N/A
5 Great fear	N/A	N/A	1 (20)	N/A	1 (5)
6 Not assessable	N/A	N/A	N/A	N/A	N/A
Not stated	2 (40)	N/A	N/A	N/A	2 (10)
How would you rate the injury risk due to unguarded training?					
1 No risk at all	3 (60)	5 (100)	4 (80)	3 (60)	15 (75)
2 No risk	N/A	N/A	1 (20)	2 (40)	3 (15)
3 Undecided	N/A	N/A	N/A	N/A	N/A
4 Little risk	N/A	N/A	N/A	N/A	N/A
5 High risk	N/A	N/A	N/A	N/A	N/A
6 Not assessable	N/A	N/A	N/A	N/A	N/A
Not stated	2 (40)	N/A	N/A	N/A	2 (10)
How would you rate the structure of the webpage?					
1 Very simple	2 (40)	3 (60)	3 (60)	2 (40)	10 (50)
2 Simple	1 (20)	1 (20)	N/A	1 (20)	3 (15)
3 Undecided	N/A	1 (20)	2 (40)	N/A	3 (15)
4 Complex	N/A	N/A	N/A	1 (20)	1 (5)

Question	iPEP[a] (N=5); n (%)	HELP[b] (N=5); n (%)	EXDEP[c] (N=5); n (%)	COMMED[d] (N=5); n (%)	Total (N=20); n (%)
5 Very complex	N/A	N/A	N/A	N/A	N/A
6 Not assessable	N/A	N/A	N/A	1 (20)	1 (5)
Not stated	2 (40)	N/A	N/A	N/A	2 (10)
How would you rate the communication with the study team?					
1 Very personal	3 (60)	5 (100)	5 (100)	3 (60)	16 (80)
2 Personal	N/A	N/A	N/A	2 (40)	2 (10)
3 Undecided	N/A	N/A	N/A	N/A	N/A
4 Impersonal	N/A	N/A	N/A	N/A	N/A
5 Very impersonal	N/A	N/A	N/A	N/A	N/A
6 Not assessable	N/A	N/A	N/A	N/A	N/A
Not stated	2 (40)	N/A	N/A	N/A	2 (10)
User satisfaction: Did the trainer support meet your expectations?					
1 Very satisfied	3 (60)	5 (100)-	5 (100)-	3 (60)	16 (80)
2 Satisfied	N/A	N/A	N/A	1 (20)	1 (5)
3 Undecided	N/A	N/A	N/A	N/A	N/A
4 Dissatisfied	N/A	N/A	N/A	N/A	N/A
5 Very dissatisfied	N/A	N/A	N/A	N/A	N/A
6 Not assessable	N/A	N/A	N/A	1 (20)	1 (5)
Not stated	2 (40)	N/A	N/A	N/A	2 (10)
Did the feedback of the trainer meet your expectations?					
1 Very satisfied	2 (40)	5 (100)	5 (100)	4 (80)	15 (80)
2 Satisfied	1 (20)	N/A	N/A	N/A	1 (5)
3 Undecided	N/A	N/A	N/A	N/A	N/A
4 Dissatisfied	N/A	N/A	N/A	N/A	N/A
5 Very dissatisfied	N/A	N/A	N/A	N/A	N/A
6 Not assessable	N/A	N/A	N/A	1 (20)	1 (5)
Not stated	2 (40)	N/A	N/A	N/A	2 (10)
Did the structure of the exercise concept meet your expectations?					
1 Very satisfied	2 (40)	4 (80)	2 (40)	2 (40)	10 (50)
2 Satisfied	1 (20)	1 (20)	3 (60)	1 (20)	6 (30)
3 Undecided	N/A	N/A	N/A	N/A	N/A
4 Dissatisfied	N/A	N/A	N/A	1 (20)	1 (5)
5 Very dissatisfied	N/A	N/A	N/A	N/A	N/A
6 Not assessable	N/A	N/A	N/A	1 (20)	1 (5)
Not stated	2 (40)	N/A	N/A	N/A	2 (10)
Give a grade for the concept (1-6 scale, 1=very good, 6=insufficient)					
1	2 (40)	1 (20)	1 (20)	N/A	4 (20)
2	1 (20)	3 (60)	3 (60)	3 (60)	7 (35)
3	N/A	1 (20)	N/A	N/A	4 (20)
4	N/A	N/A	N/A	N/A	N/A
5	N/A	N/A	N/A	1 (20)	1 (5)
6	N/A	N/A	N/A	N/A	N/A

Question	iPEP[a] (N=5); n (%)	HELP[b] (N=5); n (%)	EXDEP[c] (N=5); n (%)	COMMED[d] (N=5); n (%)	Total (N=20); n (%)
Not stated	2 (40)	N/A	1 (20)	1 (20)	4 (20)
Would you continue to use the webpage? (1-10 scale, 1=unlikely, 10=likely)					
1	N/A	N/A	N/A	2 (40)	2 (10)
2	N/A	N/A	N/A	1 (20)	1 (5)
3	N/A	N/A	1 (20)	N/A	1 (5)
4	N/A	1 (20)	1 (20)	1 (20)	3 (15)
5	1 (20)	N/A	N/A	N/A	1 (5)
6	2 (40)	N/A	N/A	N/A	2 (10)
7	N/A	1 (20)	1 (20)	N/A	2 (10)
8	N/A	1 (20)	N/A	N/A	1 (5)
9	N/A	1 (20)	N/A	N/A	1 (5)
10	N/A	1 (20)	1 (20)	1 (20)	3 (15)
Not stated	2 (40)	N/A	1 (20)	N/A	2 (15)

[a]iPEP: internet-based perioperative exercise program.

[b]HELP: hepatic inflammation and physical performance in patients with NASH.

[c]EXDEP: exercise for depression.

[d]COMMED: cystic fibrosis online mentoring for microbiome, exercise, and diet.

[e]N/A: not applicable.

Table 5 summarizes the subjective satisfaction levels with the Web-based concept. In terms of practicability and structure of the exercise recommendations, patients of the COMMED study stated a lower satisfaction level compared with the participants of the other substudies. This is also reflected in the statement for further usage of the website. Patients of the COMMED study were less interested in a continued use in contrast to patients of the other substudies. The highest interest and satisfaction with the concept could be shown in the HELP and iPEP cohort. At the end of the study, participants mentioned suggestions for improvements. These improvements were dependent on the disease and respective treatments. Thus, participants of the HELP and iPEP study asked for more information and support in nutritional aspects, whereas the younger patient cohort of the COMMED study claimed for app support and a new clear and structured design of the website.

Discussion

Principal Findings

This investigation evaluated the feasibility of the Web-based exercise concept for different diseases. The participants of all studies were able to take advantage of the information material and the individual recommendations, irrespective of types of diseases. A quick and easy access to the website enabled a continuous and regular support for the patients. However, a reduced log-in behavior (number and duration) was observed during the time course of the first 8 weeks.

In accordance to Eysenbach et al (2005), less-frequent log-in rates over time are a serious problem of Web-based interventions [42]. According to Couper et al (2007), technical challenges (eg, no access to email, problems accessing or submitting the survey) and problems with the survey (eg, lack of interest in or lack of effectiveness of intervention, no time or bad timing, survey was boring or too long) are the main reasons for noncompletion [49]. Nevertheless, the only common feature of Web-based interventions is the delivery channel [50]. Therefore, the particular role of the website must be evaluated carefully. Regardless of the underlying issue, several features could be frequently used, from computer-generated feedback and general information, such as pamphlets and regular newsletters through to fully tailored feedback and regular contact with peers and the study team (eg, chat or forum function) [51-60]. Besides regular updates, peers on the Web, and general information, the communication to a counselor and the regular monitoring of results by a professional sports therapist seem to be a key reason for compliance and adherence in Web-based settings [34,44,45,61,62]. The log-in rates or durations during the intervention period are influenced by the features offered and are of particular importance in investigations where programs for health education or behavioral change demand regular interaction. In our setting, patients obtained weekly individually tailored exercise recommendations and were encouraged to perform the training in their home environment. The exercise manual for strength training and detailed video files for each exercise could be downloaded and used offline. In accordance to Farvolden et al (2005), this opportunity could explain the high attrition rate over time [53]. Study participants of our investigations got used to the home page and probably preferred viewing the study materials offline. The patients were not obliged to log in several times a week or to be online for special appointments, to complete the study. Furthermore, the patients were able to communicate with the study team via other channels such as apps (WhatsApp), email, or phone contact. The average length of a visit was 14 min and 38 s (SD: 11 min, 29 s), and thus similar to a cognitive behavioral therapy

investigation by Farvolden et al (2005) in a collective of patients with panic disorders [53]. A comparable log-in behavior could also be seen in a Web-based physical activity investigation in a cohort of diabetes patients over an 8-week period. The average session duration was 13 min, and the investigators also identified a steep decline in usage of the program toward the end of the study [63]. On the contrary, it is particularly interesting to note that the patients with depressive disorders of our EXDEP study checked the webpage 2.6 times a week and stayed online for more than 23 min. A review article by Vandelanotte et al (2007) summarized the effects of Web-based physical activity interventions in different collectives. Physical activity improvements could be detected in 8 of 15 studies reviewed from 2000 to 2007 [57]. However, essential differences exist between support strategies and the integration of the website content [58-60]. To examine the participants' perceptions of a physical activity promotion website, Sciamanna et al (2002) provided support in terms of general information materials such as tips for overcoming barriers or instructions for measuring HR and setting activity goals [64]. Furthermore, a printable daily self-monitoring chart of physical activities was available [64]. Similar to our investigation, McKay et al (2001) provided tailored feedback on the basis of the baseline activity level [63]. Study participants received tailored messages to increase the daily activity minutes [63].

In our substudies, regular feedback and tailored recommendations were provided. However, not all study participants followed our instructions. Due to individual situations (eg, well-being vs cancer with neoadjuvant radio/chemotherapy), participants performed alternative exercise programs (eg, relaxation exercise, yoga, or hiking) instead of our recommendation. Therefore, the results in terms of exercise progress during the intervention period should be interpreted with caution. Despite the observed decline in log-in rates and durations toward the end of our substudies, most of the participants (80%, 16/20) were still satisfied with the structure of the concept, which is in accordance with the findings of McKay et al (2001) [63]. It remains unanswered by our present data whether a significant and ongoing decline in log-in behavior, as shown, necessarily means a progressive reduction in exercise adherence.

Strengths and Limitations

The main strength of this study is the easy access to the website, the opportunity to reach a large group of patients, and the possibility to provide individually tailored exercise support. Furthermore, an immediate reaction on questions, problems, or postings was feasible. Log-in data could be easily collected by tracking the account activity in an objective manner. Finally,

the intervention was free of charge and due to minimum investment in human effort, cost effective.

The fact that study participants gave subjective response on their physical activity during a week without an objective evaluation, can be seen as the main disadvantage. The study team had to rely on the participants' report. Another aspect that needs to be considered, is the website itself. Neither was the forum moderated, nor were regular newsletters distributed, and this possibly led to a reduced log-in activity. Finally, Web-based interventions do reach only selected participants who have access to the internet. Lack of control groups should also be seen as a major limitation. In addition, comparison of the single trials must be interpreted with caution due to the small sample size and the heterogeneous collectives. However, the common platform and same procedure for exercise support might show a general and uniform applicability of the concept used.

Future Research

Regular updates, intensified monitoring, moderated discussion forums, and additional information materials from other areas of interest, associated with coping with the specific disease, such as nutrition and relaxation, could be added to sustain the website usage in the long run. Furthermore, the integration of app support and modification of the website toward a more intuitive structure as well as the integration of extended functions, such as Web-based forms or data entry, should be realized with regard to subsequent investigations. Finally, investigations with other lifestyle-related diseases, mainly with the metabolic syndrome and its consequences, such as diabetes, obesity, or heart disease, should be focused upon in the future due to its rising incidence.

Conclusions

The universal use of the Web-based concept appears to be applicable across different diseases and age groups. Although the development of physical activity shows only moderate improvements, flexible communication, timely response to patients' needs, and tailored support could be easily integrated into patients' daily routine. However, because of different application habits of the website among the substudies, designing a website that is suitable and sustainable for most users will be a challenging target for future studies. Despite the existing limitations, Web-based approaches can be a helpful supplemental method to bridge the gap between inpatient and outpatient rehabilitation and home treatment for chronically ill patients. An ongoing development in telemedicine makes this kind of intervention with its cost- and time-effectiveness especially interesting for the future.

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Authors' Contributions

PS, IG, KP, JMS, YH, PJ, NH, and DP developed the individual study concepts. DP designed the website. PS, NH, and DP designed the exercise components, and PJ, IG, KL, KP, YH, and JMS revised the manuscript. All authors read and approved the final document.

Conflicts of Interest

None declared.

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Abbreviations

BMI: body mass index
COMMED: cystic fibrosis online mentoring for microbiome, exercise, and diet
EXDEP: exercise for depression

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FEV1: forced expiratory volume in 1 second
HELP: hepatic inflammation and physical performance in patients with NASH
HR: heart rate
iPEP: internet-based perioperative exercise program
NAFLD: nonalcoholic fatty liver disease
NASH: nonalcoholic steatohepatitis

Original Paper

The Development of Delta: Using Agile to Develop a Decision Aid for Pediatric Oncology Clinical Trial Enrollment

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Abstract

Background: The internet is increasingly being used to disseminate health information. Given the complexity of pediatric oncology clinical trials, we developed Delta, a Web-based decision aid to support families deciding whether or not to enroll their child with cancer in a clinical trial.

Objective: This paper details the Agile development process of Delta and user testing results of Delta.

Methods: Development was iterative and involved 5 main stages: a requirements analysis, planning, design, development, and user testing. For user testing, we conducted 13 eye-tracking analyses and think-aloud interviews with health care professionals (n=6) and parents (n=7).

Results: Results suggested that there was minimal rereading of content and a high level of engagement in content. However, there were some navigational problems. Participants reported high acceptability (12/13) and high usability of the website (8/13).

Conclusions: Delta demonstrates the utility for the use of Agile in the development of a Web-based decision aid for health purposes. Our study provides a clear step-by-step guide to develop a Web-based psychosocial tool within the health setting.

Introduction

Decision Making Regarding Pediatric Oncology Clinical Trials

Many parents are faced with the decision of whether to enroll their child with cancer in a clinical trial. In Australia, approximately 80% of children with cancer enroll in a clinical trial. Despite the necessity of clinical trials to test new treatments with the aim to find more effective cancer treatments, patients and parents often find the decision difficult [1,2]. Families often find the rationale, design, and long-term implications of participating in trials difficult to understand [3]. Early phase clinical trials can be particularly confusing, with parents and young people overestimating the potential benefit of the trials (called therapeutic misconception) [4,5], making it difficult for them to weigh up the benefit and burden of enrolling while hoping for a cure. Deciding whether to enroll is also complex, given the time pressures to proceed to therapy, the large amount of information to comprehend, and the emotional timing of the

decision, which is often at either diagnosis or relapse. Many families experience decisional anxiety and uncertainty and psychological distress associated with the decision whether to enroll their child in a clinical trial or not [1,6].

With clinical trial decisions, there may not necessarily be a *right or wrong* choice of treatment. In these scenarios, individual values and preferences of the family become crucial. Decision aids are evidence-based tools designed to assist clients to be involved in making specific and deliberated choices among health care options [7]. Decision aids support patients and caregivers to make informed decisions by helping them to balance their values with the benefits and disadvantages of their treatment options. The "International Patient Decision Aid Standards" (IPDAS) highlight the role of clear information of treatment options based on research evidence, opportunities to clarify and express values, structured guidance in deliberation and communication of choice, and developed using a systematic development process [8]. Although decision aids vary in formats, decision aids appear to improve knowledge, quality of informed consent, and decision satisfaction for adult patients making treatment or screening decisions (eg, prostate cancer screening, menopausal hormone therapy) [9]. An evaluation of a decision aid in adult cancer clinical trials ("Cancer Research Choices") has also shown reduced decisional conflict and postdecision regret compared with standard of care, without impacting clinical trial enrollment rates [10]. Despite the fact that some decision aids exist in adult clinical trials, none are available in pediatric oncology.

Agile Development Process

Agile development is an overarching term to describe a software development process. Agile focuses on collaborations between developers and stakeholders, flexible methodology, and the ability to respond quickly to change through multiple iterations [11,12]. Changes even in late development are encouraged. This approach aims to deliver a product that can quickly adapt to clients' changing needs and also deliver a high-quality and high-value project within the constraints (ie, cost, schedule, and scope) [13].

The use of Agile approaches has an increasing worldwide use within software development [14,15] and research [16]. Use of Agile approaches has been reported to result in higher business performance, customer satisfaction, and product quality compared with more structured nonfluid approaches [17]. Agile projects were reported to be 28% more likely to succeed (defined by a project that is completed on time and budget and includes originally outlined specifications) [18]. Multiple case studies have acknowledged the challenges of implementing Agile development, such as highly intensive interactions with stakeholders [19], however many have reported an overall positive impact [20-23].

In recent years, there has been a rapid growth in the use of, and access to, the internet for health purposes [24,25]. In Australia, studies have reported over 28% of patients access Web-based health information [26], and in the United States, more than 43% do [27]. In Swedish adult cancer patients, approximately 77% of patients seek Web-based health information [28].

Accessing health information in oncology has been reported to improve oncologist-patient communication and connectedness, patient use of medical jargon, and scientific knowledge [29].

Given the movement toward a more patient-centered and collaborative decision making approach in the health care system [30], there is a rising need for innovative product development that is provided online and tailored to the patient and their family. The principles of Agile are an appropriate vehicle to guide the development of a Web-based patient decision aid, especially those with clear aims yet flexibility in design [11].

Methods

Using Agile to Develop Delta

We developed Delta, a Web-based decision aid to support families deciding whether or not to participate in a pediatric oncology clinical trial. The main of aim of Delta was to improve clinical trial knowledge and facilitate treatment discussions and shared decision making between families and health care professionals (HCPs). Families offered a clinical trial are able to log in to the Delta website, which links to the clinical trial they are considering. Delta incorporates general content about clinical trials (eg, what are clinical trials, how do clinical trials work), the specific clinical trial information sheet, and a values clarification exercise. This paper provides a detailed description of the development and early testing of Delta, acting as proof of concept for the use of Agile for the development of a Web-based decision aid.

The development of Delta was divided into the 5 main stages involved in Agile development and was both iterative (with one iteration referring to revisions made on one particular version of the website following feedback) and incremental (see Figure 1). We expected development to take 4 months from approval of the functional specification, with an additional 2 months for prepilot user testing. Due to delays in development and complexity of using Agile in research (see Discussion section), the actual development time of Delta was approximately 4 months of full-time work and 2 months of user testing, spread over 12 months. Our development was driven by guidelines for patient websites [31], the International Patient Decision Aid Standards (IPDAS) [7], and 12 Agile principles (see Multimedia Appendix 1).

The development of Delta was supported by a steering committee (16 members) to ensure development followed IPDAS [7]. The committee included psycho-oncology researchers (n=6), pediatric oncologists (n=5), a pediatric oncology clinical trial research manager (n=1), a clinical nurse consultant (n=1), parents (n=2), and a young person with cancer (n=1). All consumers signed a Terms of Reference Agreement specifying the purpose of the committee and their role. As Agile leans toward a leadership and collaboration approach, where a team leader acts as a facilitator, we also established a lead development team (3 members) from the steering committee to provide more regular feedback (ER, CW, and JF). The lead team met with each other face-to-face fortnightly, and all steering committee members met on an as-needed basis.

Figure 1. Delta development process. Estimated time is based on full days of work required, which occurred over a 12-month period.
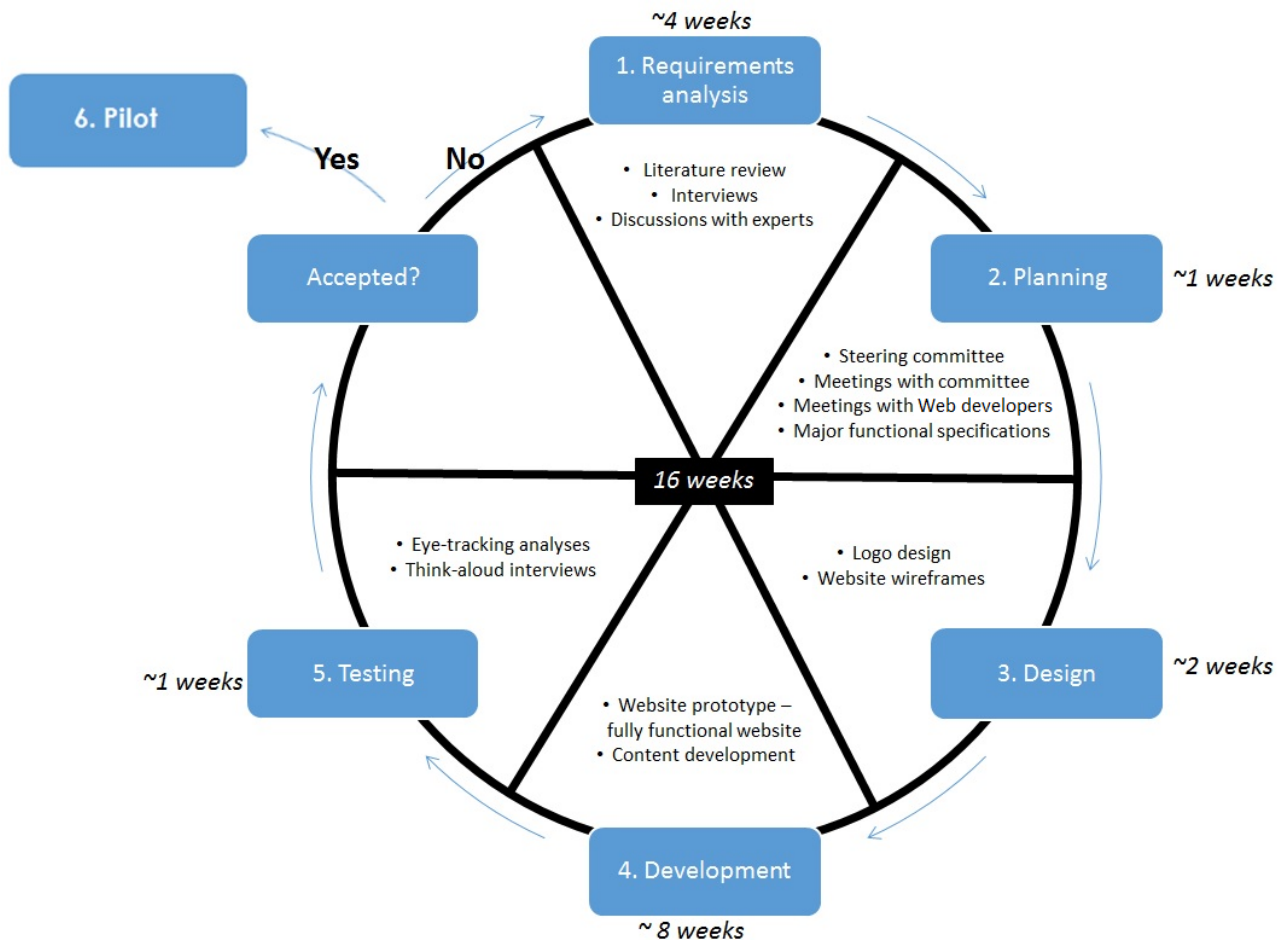
Requirements Analysis

Requirements analysis was required to identify the needs and preferences of families in regard to information and functionality of the website. We identified needs and preferences of families by conducting a basic literature search, leading a systematic review on strategies to facilitate shared decision making in pediatric oncology clinical trials [32], and through discussions with the steering committee. Our team also conducted interviews with 25 Australian parents and 5 adolescents recently diagnosed with cancer to identify the needs and preferences of families when making treatment decisions. We continued the requirements analysis throughout the whole development process via discussions with the steering committee and literature searches.

Planning

Planning was required to determine appropriate timelines for the completion of sprints (ie, smaller milestones to be completed and reviewed in short time frames), content and website functions, and design. We chose Web developers based on their experience, reputation from previous clients, corresponding values in development ideologies, cost of deliverables, and workable time frames. Planned sprints, between 2 and 4 weeks, were also agreed upon based on workable time frames of the lead team and Web developers. A lead team member (ER) developed the content framework and the ideal design and functionalities of the website, which was approved after 3

iterations by the other lead team members. ER met with Web developers face-to-face on 3 occasions before beginning development to discuss the website concept, functional specifications, and website requirements. Web developers then finalized the functional specification, which the lead team approved.

Design

The design stage involved design of the Delta logo, color scheme, font, and graphics and website wireframes (ie, a visual display of the function and framework of the website). A graphic designer with a good working relationship with the lead team assisted with these tasks. The logo and color scheme went through 2 iterations before approval by the lead team and steering committee. ER developed wireframes following the initial planning with the Web developers. Wireframes went through 3 iterations with the lead team before beginning functional website protocol development. Web developers then developed the website prototype. We asked all steering committee members to provide feedback on the website prototype. We implemented suggested modifications based on consensus.

Development

The development stage involved the development of content and the functional Delta website. We developed Delta to be highly scalable, both horizontally (ie, ability to add more resources, such as content) and vertically (ie, ability to increase

the functionality or capacity, such as potential functionality as an app). Delta has a responsive Web design. It has been developed to be user-friendly across multiple platforms, including computers, tablets, and mobile phone, and has in place the capability to be scaled up to be available as an app. Although currently only in English, it also has the capability to be scaled out to be available in multiple languages. Delta can also be easily scaled out by allowing the addition of as many clinical trials as necessary. The method to add in additional clinical trials has been simplified to ensure Delta is easily maintainable. We also ensured Delta was developed with a content management system, which allowed content to be easily updated without the need for Web developers.

Content Development

Content went through approximately 8 rounds of iterations across 6 months, before being embedded within the website. We developed 2 versions of Delta (one version for parents and one for adolescents aged 12 years and older). Our systematic review [32] identified 3 key strategies to facilitate shared decision making in pediatric oncology: (1) quality information exchange, (2) clear communication, and (3) decision making support. We developed Delta to incorporate these 3 core features of shared decision making [32]. We developed Delta to cater for low health literacy populations. To facilitate information exchange, we presented information at Grade 8 readability for parent content [33] and Grade 5 readability for adolescent content. The reader is able to access less or more detailed information based on their preference for information amount. We provided an option grid for readers to easily compare key information between their options. We also acknowledged the role of gist memory (that is, recall of bottom-line meaning rather than detailed information) and therefore included summary boxes of information. To promote communication, we incorporated a question prompt list and suggested strategies for parents to communicate with HCPs and their child (if appropriate).

To provide more decisional support, we incorporated a values clarification exercise. A values clarification exercise allows participants to clarify and communicate the personal value of options, to ultimately make a better quality decision [34] that is most personally desirable [35], and results in less decisional regret [36]. The Delta values clarification exercise allows parents to rate their reasons to enroll or not to enroll in the clinical trial on a scale of personal importance. Delta is able to show whether the parent appears to be leaning toward enrolling in the trial or not. As per many patient decision aids [37], the algorithm for the outcome of the Delta values clarification exercise is basic, providing a summation of participant responses. Although items may be weighted differently for each participant, the purpose of the decision making exercise is not to provide a *correct answer* or a *recommendation*, but rather allow participants to weigh up their treatment options. Participants are instructed that this exercise will provide some indication as to the option they are more inclined to choose, but to discuss it further with their treating team.

Delta also provides the specific information sheet for the clinical trial in which the family was invited to participate. The website also includes a glossary, a text-to-speech function, and the ability to save and print notes from within the website. See Table 1 for the key elements of Delta.

Web Development

Web developers delivered progress in fortnightly or monthly sprints. The lead team provided feedback of the sprints, and Web developers made necessary modifications as they came up. For the final sprint, of the 16 steering committee members, 12 were available to provide feedback. Modifications suggested by the steering committee were discussed with the lead team and implemented based on consensus. We received multiple iterations of the website in early stages of development from steering committee members. During later stages of development, the lead team requested less feedback and thus had fewer iterations. Fewer iterations in later development were due to significant delays in development and the minimal value that later iterations provided (eg, minor wording changes). See Multimedia Appendix 2 for a video introduction to the Delta website.

Table 1. Key elements of Delta, categorized by function and health literacy needs.

Element	Strategy theme[a]	Health literacy[b]
Information about clinical trials (grade 8 readability and minimal medical jargon)	Information provision	Functional
Specific clinical trial information sheet	Information provision	Functional
Interactive glossary	Information provision	Functional
Text-to-speech functionality	Information provision	Functional
Question prompt list	Communication	Communicative
Personal notes page	Communication	Communicative
Communication strategies	Communication	Communicative
Values clarification exercise	Decision making support	Critical

[a]Strategy themes were identified via our systematic review [32].

[b]Health literacy categories are based on Nutbeam's model of health literacy [38].

User Testing

We conducted eye-tracking analyses to assess the usability of the Delta website. Eye-tracking analyses have frequently been used in website development [39,40]. The analysis used a computer with an embedded webcam to track each participant's point of gaze. We conducted eye-tracking analyses to determine where participants' gaze lingered, their length of gaze, and readability (ie, scanning, reading, or rereading of content). Data collected through eye-tracking analyses can be presented as either a gaze plot or a heat map. Gaze plots show the location, order, and time (known as the fixation duration) spent looking across certain aspects of the website. Heat maps are a visualization of the focus of visual attention across multiple participants.

We also conducted retrospective think-aloud interviews to establish participant satisfaction and acceptability of the website. Retrospective think-aloud interviews encourage participants to verbalize aloud their thought processes on replay of their task completion and are commonly used in website development [41,42]. The literature suggests 5 to 9 participants in think-aloud interviews, and eye-tracking analyses can detect 80% to 90% of usability problems on a website [43,44].

Individuals were eligible to participate if they were a parent of a child treated for cancer at Sydney Children's Hospital. ER undertook user testing in a private office at the Sydney Children's Hospital. Participants were all experienced at using computers and the internet. Participants were reimbursed with an Aus $20 gift voucher. The local ethics committee approved the user testing.

We instructed participants to browse the website for a maximum of 40 min. We asked participants to view the website as if they had had a consultation with their clinician regarding enrolling in a clinical trial and then provided with the Web-based decision aid. We emphasized to participants that the goal was not to assess their computer skills or their knowledge of clinical trials but rather to test the usability and acceptability of the website. If participants did not view the values clarification exercise of their own accord, ER directed the participant to complete it.

Following the free browsing of the website, ER asked basic questions regarding usability, functionality, and acceptability of the website. We used a retrospective think-aloud protocol. This involved participants thinking aloud their thought process alongside a visual replay of their own eye-tracking data.

Results

User-Testing Results

A total of 17 families were identified as appropriate to contact by an oncologist or nurse (see Table 2 for participant demographics). Moreover, 7 parents opted into the study (all mothers). Reasons for nonparticipation included being too busy or living too far away to come to the hospital. Eye-tracking data are missing for one parent because of technical difficulties. A total of 6 HCPs in psycho-oncology (4/6 females) also participated in user testing.

Eye gaze was detectable, on average, 93% of the time. Validity of the gaze for both the left and right eyes was 0 on average, suggesting that the tracking quality was good. Participants left-clicked 142 times on average (range 86-237 clicks). Participants took 50.1 s to log in to the website (SD 31.0; range 25-133), 14.3 min on average to read the general content of decision aid (SD 9.5; range 2.1-33.6), and 2.5 min to complete the values clarification exercise (SD 0.9; range 1.1-4; see Table 3 for an overview of data).

Most participants completed the values clarification exercise (5/6 HCPs; 6/7 parents), with 5 participants (4 HCPs, 1 parent) accessing the exercise without being prompted. The reasons participants did not access the exercise was because they did not see the link to access the exercise (n=4 parents) or did not feel it was relevant to them (n=1 HCP). One HCP completed the exercise twice as they wanted to see if their responses changed after reading more information. The methods of accessing content were to use the side panel menu (n=3 HCPs, n=3 parents), the "next" button (n=1 HCPs, n=2 parents), a combination of both (n=2 HCPs), or the home button (n=1 parent).

Table 2. Summary of parent participant characteristics.

Parental role	Child age at diagnosis	Time since child's diagnosis in months	Clinical trial[a]
Mother	12	12	No
Mother	7	12	Yes
Mother	6	11	Yes
Mother	0.5	54	Yes
Mother	7	33	Yes
Mother	5	58	Yes
Mother[b]	13	6	Yes
Average (SD)	7.2 (4.2)	26.6 (21.9)	N/A[c]

[a]Families who were enrolled in a clinical trial as part of their child's cancer treatment.

[b]Eye-tracking data are missing for this participant because of technical issues.

[c]N/A: not applicable.

Table 3. Overview of time to complete tasks.

Tasks	Overall (n=12)		Parent (n=6)		Health care professionals (n=6)		t value[a] (degrees of freedom)
	Average time (SD)	Range	Average time (SD)	Range	Average time (SD)	Range	
Log in time	50.1 s (31.0)	25-133 s	64.4 s (40.8)	27-133 s	38.2 s (14.9)	25-65 s	−1.475 (9)
Reading general content	14.3 min (9.5)	2.1-33.6 min	13.7 min (7.3)	5.3-24.0 min	14.8 min (12.0)	2.1-33.6 min	0.181 (10)
Completing the values clarification exercise	2.5 min (0.9)	1.1-4 min	2.8 min (0.7)	1.8-3.7 min	2.1 min (1.0)	1.1-4 min	0.424 (10)

[a]No comparisons were significant.

Most participants reported high acceptability (5/6 HCPs; 7/7 parents) and high usability of the website (4/6 HCPs; 4/7 parents):

> It was nice and clear. It was simple. It had a good flow, not too many buttons to make you completely overwhelmed. Your emotions would be ridiculously high if you are looking at this, so you need to make it as simple as possible, so I like that there are three main parts to it [Parent of a 5-year-old boy with neuroblastoma]

Most participants (5/6 HCPs; 6/7 parents) found the content easy to read and reported that it flowed logically. Some participants read the summary boxes before reading the main content (2/6 HCPs; 2/7 parents). These participants chose to read that section first as they felt it would be the most important information. Minor word changes were suggested by all participants (eg, change "me time" to "self-care"). None of the participants used the personal notes function, however several freely reported in the think-aloud interview that this function would be useful (n=1 HCP; n=3 parents). Moreover, 7 participants used the glossary (n=3 HCPs; n=4 parents), reporting the usefulness of the function. No participants used the speech-to-text function.

There were few instances of rereading of content, with eye-tracking data suggesting that participants read lines to completion (see Figure 2). Most participants (5/6 HCPs; 6/6 parents; n=1 missing parent) skipped at least one page of content. Participants skipped content as they either did not want to read that information (1/5 HCPs; 1/6 parents) or did not realize they had skipped it (4/5 HCPs; 5/6 parents). Participants suggested that reducing overlap of images and phrases would improve usability. There were some particularly long fixations throughout the website, which is indicative of cognitive processing. Examples of long fixations include the terms "antitumor activity" and "dose escalation" (see Figure 3).

Most participants reported at least some difficulty in navigating the website (3/6 parents; 4/7 parents). Problems included finding the home page and accessing more content. Eye-tracking data suggested that once participants were more familiar with the website, they were easily able to navigate to the next page of content (see Figure 4). In think-aloud interviews, many participants felt that they would have found navigation easier if font and icons were of a larger size and darker color (2/6 HCPs; 6/7 parents). Participants found the values clarification exercise useful, and the participants' suggested leaning reflected how they felt they were leaning with regards to whether or not to enroll their child in the clinical trial (4/5 HCPs; 6/7 parents):

> I think the tool is a helpful way to make a decision. It shows you from the way you've answered the questions that you are tending, even if you feel undecided. It gives you options to further think about "Why am I tending that way?," "What don't I actually like about the trial?," and "What more information do I need?" [Mother of a 10-year-old boy with neuroblastoma]

> After this tool, we would really start talking with each other. The exercise is great—it becomes a tool at that point for more people to really engage. [Mother of a 13-year-old boy with osteosarcoma]

Eye-tracking analyses showed long fixations for the first few values clarification exercise items and scale. Less time was spent on the last two items of the exercise, suggesting cognitive fatigue. In think-aloud interviews, participants reported feeling unsure of how to use the values clarification exercise (2/5 HCPs; 2/7 parents). Only 5 participants (all HCPs) accessed instructions on how to complete the exercise, with minimal gaze focusing on the instructions panel (see Figure 5). However, most participants (4/6 HCPs; 6/7 parents) found that the exercise was useful and accurate in the direction they felt they were leaning:

> I was really impressed—I wasn't expecting that. It was great. The outcome of enrolling in the clinical trial was how I was feeling. It's still interesting to see that sentence come up and say that that though [Mother of a 9-year-old girl with acute lymphoblastic leukemia]

Participants felt that the user experience of the values clarification exercise could have been improved by providing a clearer introduction and purpose of the exercise (2/6 HCPs; 4/7 parents) and providing more visible instructions (1/6 HCPs; 7/7 parents). See Table 4 for an overview of user testing findings.

Implementation of User Testing Findings

User testing revealed that both HCPs and parents found Delta to be acceptable and useful. On the basis of the results of the user testing, the lead team reviewed the changes suggested and implemented changes based on consensus. Main changes included replacement of the "home" icon and darker and larger font. See Table 5 for summary of main modifications made. Although some minor issues were raised, overall findings were positive.

Figure 2. Gaze plot of one participant. Circles represent the gaze or fixation of the participant, with larger circles indicating longer fixations. Circles are numbered based on the order of fixation. The line between each fixation point represents the saccade or rapid movement between each fixation. This participant is reading lines from start to finish and appears to understand content as there are few long fixations. Only one participant was able to be used in this gaze plot as Delta is a scrolling website, and other participants did not stop their webpage in the exact same location.
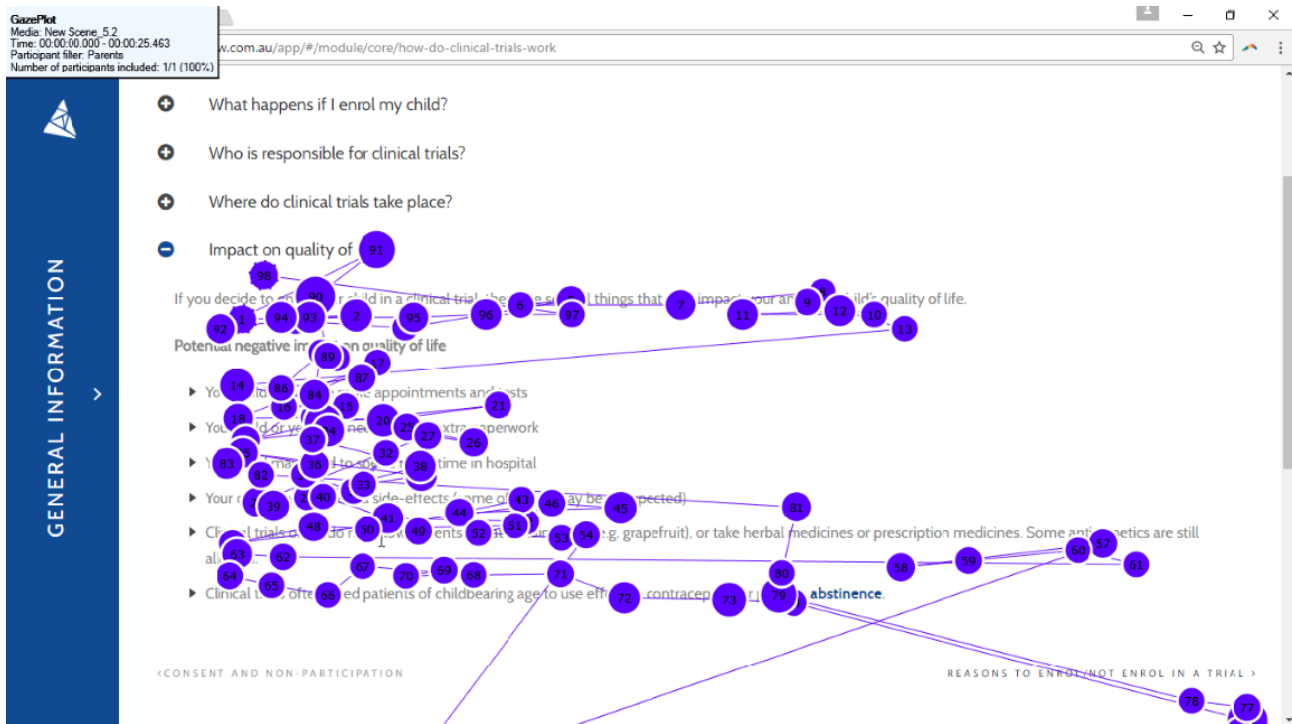
Figure 3. Heat map of one participant. Color represents the length of gaze, with deep red indicating longer fixations. Longer fixation on "antitumor activity" suggests higher levels of cognitive loading and potentially reduced comprehension.

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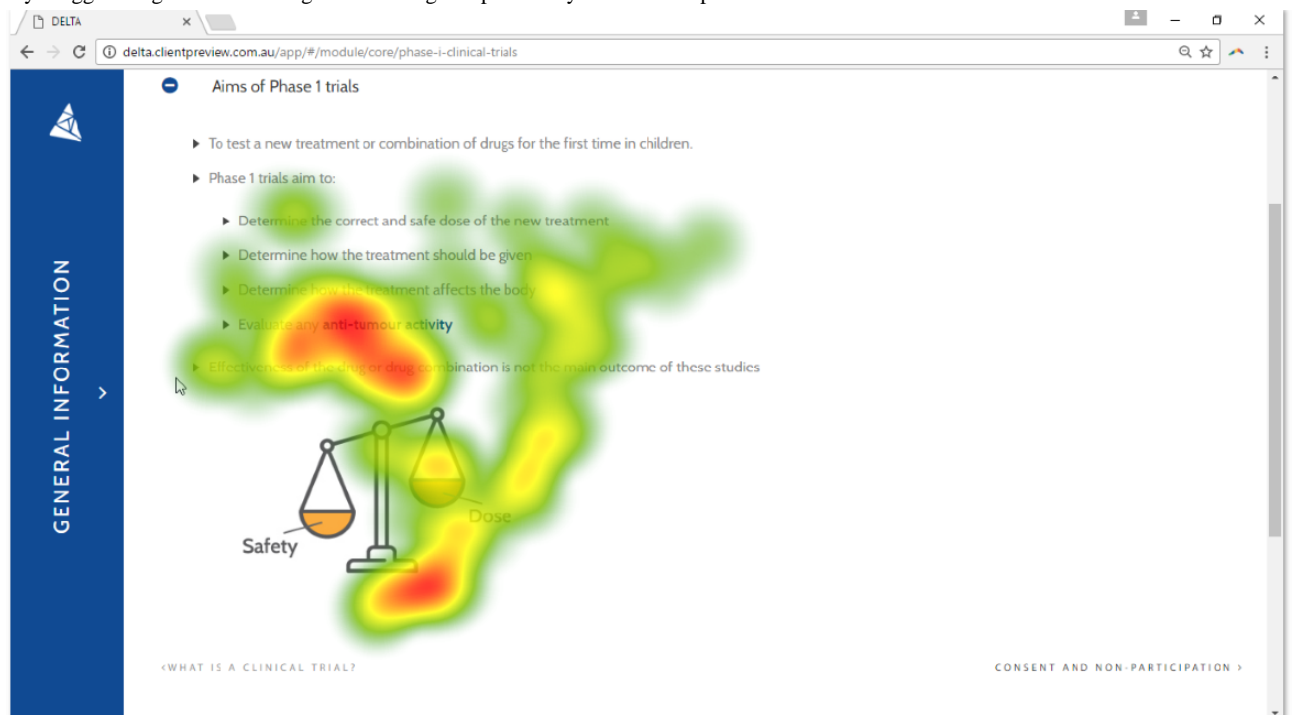
Figure 4. Gaze plot of 2 participants. Different colored circles represent each participant. Circles represent the gaze or fixation of the participant, with larger circles indicating longer fixations. Circles are numbered based on the order of fixation. The line between each fixation point represents the saccade or rapid movement between each fixation. Both participants appeared to be able to easily see the "next" button to navigate to more content. Only 2 participants were able to be used in this gaze plot as Delta is a scrolling website, and other participants did not stop their webpage in the exact same location.
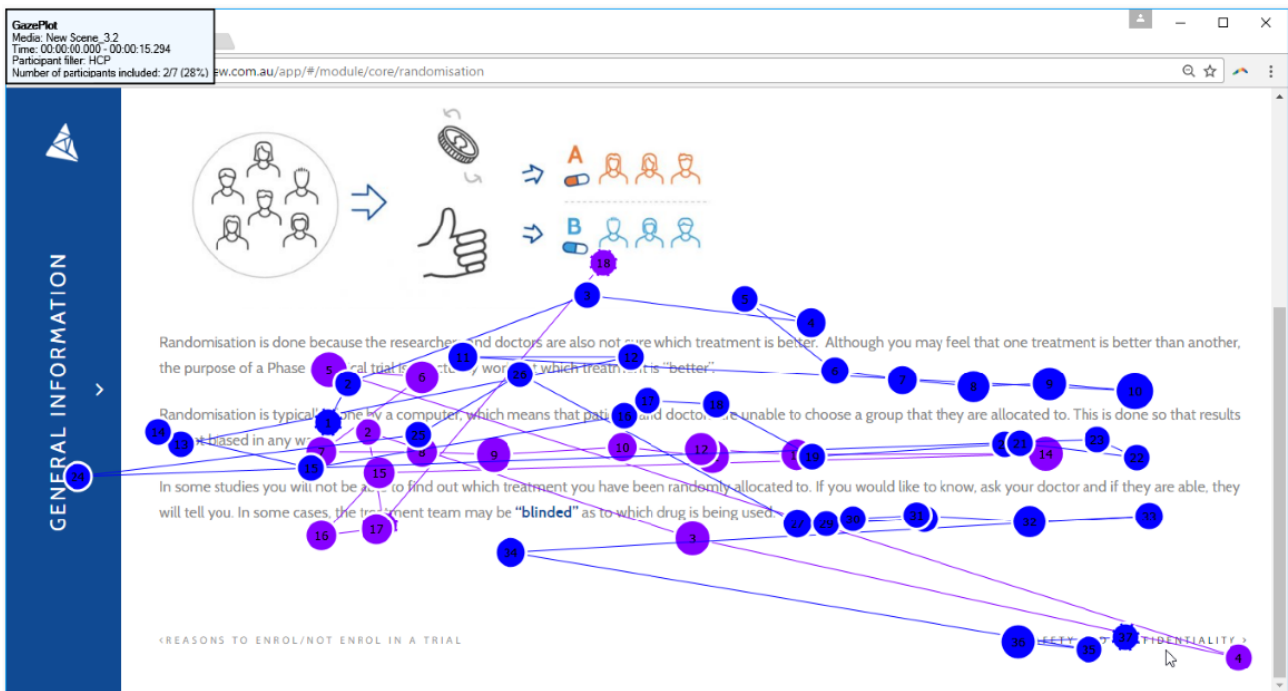
Figure 5. Gaze plot of 8 participants. Different colored circles represent each participant. Circles represent the gaze or fixation of the participant, with larger circles indicating longer fixations. Only 3 participants gazed at the instructions panel on the far left, for a minimal fixation length. Only 8 participants were able to be used in this gaze plot as Delta is a scrolling website, and other participants did not stop their web page in the exact same location.
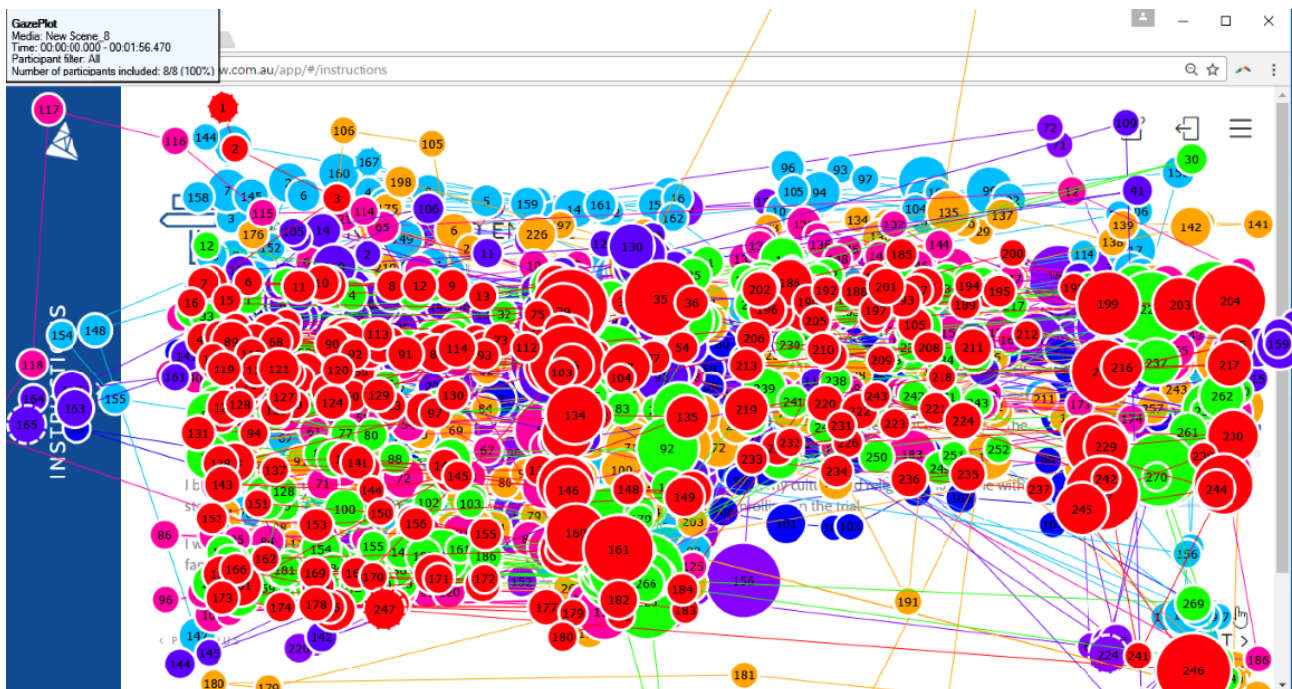
Table 4. Number of health care professionals (HCPs) and parent who used each Delta function.

Delta functions	Overall (N=13)	HCPs (N=6)	Parent (N=7)
Values clarification exercise			
Completed values clarification exercise	12	5	7
Completed task without being prompted	5	4	1
Found exercise was accurate and useful	10	4	6
Viewed instructions for exercise	5	5	0
Accessing content			
Side panel	6	3	3
Next button	3	1	2
Combination of side panel and next button	2	2	0
Home page	1	0	1
Acceptability and usability			
Reported high acceptability	12	5	7
Reported high usability	8	4	4
At least some minor navigational issues	7	3	4
Suggestion for larger and darker font	8	2	6
Content			
Content easy to read	11	5	6
Minor word changes suggested	13	6	7
Read summary boxes first	4	2	2
Used notes function	0	0	0
Used glossary function	7	3	4
Used text-to-speech function	0	0	0
Skipped at least one page[a]	11	5	6

[a]Data missing from 1 parent.

Table 5. Main modifications based on eye-tracking analyses and think-aloud interviews.

| Area[a]	Modification
Content	Minor wording changes made throughout website
Content	Reduction of overlap of content throughout
Content	Clear introduction of purpose of values clarification exercise
Design	Home page more obvious to navigate
Design	Darker color and large-sized font
Design	Values clarification exercise instructions more obvious

[a]Modifications were related to either content or design.

Some of the features within the website were not used (eg, notes page) or were used by approximately half of the sample. We expected this level of use, given that approximately half of the features and functions are used in a typical website [13].

User testing findings should be considered in light of several limitations. We were only able to recruit mothers for this study. However, this may be appropriate feedback, given that mothers tend to take on a greater decisional role than fathers in pediatric oncology [45]. Our findings may also be biased because of our sample having more interest in participating in such research. Finally, as Delta involves pages that scroll, we cannot guarantee the precise accuracy of the eye-tracking analyses in regard to the gaze plots and heat map outputs. Although feedback regarding Delta was positive, we cannot assure ecological validity in that parents would actively engage with the content outside of the user testing given the potential of the Hawthorne effect.

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Discussion

Study Overview

This paper details the development of Delta, a Web-based decision aid to support families to decide whether or not to enroll in a pediatric oncology clinical trial. We developed Delta using the Agile approach, which included a requirements analysis, planning, design, development, and user testing. We developed Delta iteratively, focusing on short sprints of work. Delta is the first a Web-based decision aid, to the authors' knowledge, developed using the Agile approach.

Benefit of Using Agile in Developing a Web-Based Psychosocial Tool

The benefit of using Agile in the development of Delta has allowed for a high level of collaboration between the lead development team, HCPs and researchers, and consumers. In research projects, such as Delta, collaborators are often chosen based on their individual expertise. This aligns well with Agile, as the success of Agile projects is largely dependent on the expertise of the team involved [46].

Involving consumers throughout development and in user testing has been especially important for Delta. The World Health Organization Declaration of Alma Ata states that "people have the right and duty to participate individually and collectively in the planning and implementation of their health care" [47]. When developing patient tools, especially for vulnerable populations as the case for Delta, patients' and families' roles should play an active role [48]. The Agile process caters for consumer involvement. Involving patients and families in the development of patient information material may result in more appropriate, sensitive, readable, and understandable information [49]. For Delta and similar research projects, this means that the limited funds available are available to be spent on what is considered most important for families and clinicians.

The benefit of using Agile in the development of Delta has also been in working in short sprints and iteratively. This means that smaller aspects of the website were presented to the developmental team, followed by iterative refinement. Short sprints mean that required changes were usually minor and thus more financially manageable. For Delta, minor issues such as reorganization of content were able to be resolved early into development. Breaking Delta into more manageable units also meant that we were able to focus on detailed yet high-quality development. Quick releases are a major benefit of using Agile [50]. Being able to deliver short sprints of work has encouraged collaborators to become more engaged, provide quality feedback, and ensure deadlines are being met.

Barriers to Using Agile in Developing a Psychosocial Tool

One of the major limitations of using Agile to develop Delta is because of the slow-moving nature of research. This has limited the ability for short and fast sprints of work. To ensure high quality of product, involvement of clinicians and consumers has been imperative. We constantly adapted our time frames to work within the constraints of the experts involved. The Delta steering committee, however, found difficulties in maintaining constant face-to-face meetings. Agile may be difficult when working with larger teams, especially with more than 20 to 30 members [50]. Even with a team of 13 members such as with Delta, issues arose in regard to meeting deadlines for feedback and having too many meetings. To overcome the difficulty in obtaining feedback at each iteration, we allocated certain tasks to team members based on their expertise and interests. The very hierarchical approach that Agile takes to development may also not work within some workplace cultures [46]. Organizations that have greater bureaucracy and formality may also experience difficulty in fast sprints of work.

With multiple iterations, the project scope is subject to change. Creating accurate budgets and schedules at the start of the project is difficult. For Delta, over the course of development, the scope of the website has almost doubled, from originally being a purely parent website to now including both parent and adolescent versions. Although Agile has allowed for scope creep in a more controlled and manageable manner, the change in scope has been costly and needed to be better budgeted. Some functions that were implemented during early cycles of development can also become redundant as requirements and scope change. The redesign and recoding can add significant costs.

For Delta, we were required to obtain ethics approval to conduct user testing, which pushed back the schedule by several weeks. Difficulties with recruitment, such as booking in times for families to complete the testing at the designated location, also delayed user testing. When working with patients and families, researchers need to be aware of the time to recruit and to conduct user testing.

Although discussions with experts and the literature have guided the development of Delta, sometimes this does not always turn out to be what is logistically possible or what families want. Agile focuses on consumers' and development teams' preferences, which meant there was an emphasis on the functional requirements of Delta (eg, text-to-speech function, glossary, and wording). The Research-Based Web Design and Usability Guidelines also encouraged us to consider nonfunctional requirements. Nonfunctional requirements include horizontal (ie, ability to build out and be produced in a variety of capabilities, such as Delta on a computer and also mobile phone compatible) and vertical scalability (ie, increasing resources or capabilities on a single component, such as Delta), security, maintainability, and longevity of Delta. However, when working with Agile, researchers should balance consumer preferences with usability and performance.

Future Directions

We recommend that researchers can develop a Web-based decision aid using Agile. We suggest that researchers set deadlines for iterations of sprints of work even in the case that the planned work may not be completely finished [51]. We strongly recommend that the 10th Agile principle of "simplicity" (ie, getting "just" enough done as needed for right now) be incorporated. We suggest that if only minimal feedback is provided by a set deadline, development continues as per these deadlines. Given the increase in value after a certain number of

iterations reaches saturation [13], this may ultimately reduce the "time-to-market" without impacting quality of work. However, it must be noted that although these deadlines are technically "set," they do require constant updating in regard to priorities and expected time for completion as the project progresses. We suggest having a *product backlog* of what has been completed and what needs to be done. The product backlog should acknowledge the value (ie, how useful or important is this as part of the project?) and the size (ie, how difficult or long development is expected to take?) of developing the feature or function. Better understanding the value and size can allow researchers to predict the return on investment and potentially reduce costs where possible. The *product backlog* should also note the velocity (ie, the rate of progress or time to complete an iteration) to ensure progress continues at an appropriate pace. We have included a suggested template for reporting the product backlog (see Multimedia Appendix 3). We also suggest future

researchers' budget for multiple iterations throughout development, both in regard to time and cost.

Conclusions

This paper provides an overview of the development and early testing of Delta, a patient Web-based decision aid for pediatric oncology clinical trial enrollment. We developed Delta using the gold standards of patient decision aids and Web development. In development of decision aids specifically, there is a definite need for guidelines or examples of development processes [52]. This paper has begun to fill this gap in the literature, providing more guidance for researchers looking to develop a Web-based decision aid. Delta acts as proof of concept of the use of Agile for the development of a Web-based decision aid. Aspects of Agile development may be useful to incorporate to ensure the development of a high-quality and high-value project within the constraints of cost, schedule, and scope. The development process detailed in this paper provides a suggested template from which future tools can be developed.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Table of Agile principles and translation to the development of Delta.

[PDF File (Adobe PDF File), 27KB - resprot_v7i5e119_app1.pdf]

Multimedia Appendix 2

Video providing an overview of the Delta website and user-testing.

[MP4 File (MP4 Video), 32MB - resprot_v7i5e119_app2.mp4]

Multimedia Appendix 3

Table providing recommended backlog template for future researchers.

[PDF File (Adobe PDF File), 23KB - resprot_v7i5e119_app3.pdf]

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Abbreviations

HCP: health care professional
IPDAS: International Patient Decision Aid Standards

XSL•FO
RenderX

Original Paper

Recruitment and Participation of Recreational Runners in a Large Epidemiological and Genetic Research Study: Retrospective Data Analysis

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Abstract

Background: With the increasing capacity for remote collection of both data and samples for medical research, a thorough assessment is needed to determine the association of population characteristics and recruitment methodologies with response rates.

Objective: The aim of this research was to assess population representativeness in a two-stage study of health and injury in recreational runners, which consisted of an epidemiological arm and genetic analysis.

Methods: The cost and success of various classical and internet-based methods were analyzed, and demographic representativeness was assessed for recruitment to the epidemiological survey, reported willingness to participate in the genetic arm of the study, actual participation, sample return, and approval for biobank storage.

Results: A total of 4965 valid responses were received, of which 1664 were deemed eligible for genetic analysis. Younger age showed a negative association with initial recruitment rate, expressed willingness to participate in genetic analysis, and actual participation. Additionally, female sex was associated with higher initial recruitment rates, and ethnic origin impacted willingness to participate in the genetic analysis (all *P*<.001).

Conclusions: The sharp decline in retention through the different stages of the study in young respondents suggests the necessity to develop specific recruitment and retention strategies when investigating a young, physically active population.

Introduction

Large-scale recruitment for research studies is now more easily achieved because of the internet [1]. In addition, new technologies simplify genetic research by enabling unassisted sample collection in the participant's own home [2]. However, when compared with the traditional recruitment methods, the distance imposed by this methodology challenges sampling bias as well as the ability to provide individualized information to participants for informed consent. Additionally, this method may hinder the development of trust, which according to some authors aids in recruitment to genetics studies [3,4].

Internet-Based Recruitment for Research Studies

Internet-based sample collection has become commonplace for health research studies. For example, a recent systematic review covered 110 studies that used Facebook to recruit up to 12,000 adult participants per study [5]. Given this trend, it has been recommended that recruitment strategies in research studies are evaluated and reported [6]. Overall, recruitment analysis conducted to date has assessed studies designed to evaluate specific health conditions or the general population, and some authors have studied the association between participants' physical activity and recruitment success [3]. However we are not aware of any research studies that have analyzed recruitment success and the efficacy of different strategies to recruit participants from a physically active population.

Participants' Attitudes to Genetic Data Collection

Clinical data belong to an individual's sensitive personal information, and genetic data pose specific ethical and security concerns for participation in research projects [7]. Studies show that the public appears to have a positive view of genetic research; however, this may not be associated with actual willingness to participate in a genetic study [8,9]. Demographic factors such as sex, age, education, and ethnicity have shown varying degrees of association with declared willingness to participate or actual participation in genetic research [10,11]. The informed consent process needs to address the concern for privacy intrusion by presenting information to participants in a clear and simple way [7], and the potential obstacles of Web-based contact in this regard warrant a specific evaluation [9]. All of these factors need to be reported to improve our management of research studies [12].

To our knowledge, the AIS (Australian Institute of Sport) Running Injury Study is the largest genetic study to date conducted on a physically active cohort [13,14]. The analysis presented here had two aims: (1) to assess the success and demographic representativeness of different recruitment strategies and (2) to highlight subject's characteristics associated with declared willingness to participate and with actual participation in the genetic arm of the study.

Methods

Overview

The AIS Running Injury Study was an initiative of the AIS and the Collaborative Research Network for Advancing Exercise and Sport Science in response to the dramatic increase in recreational running in Australia in the past decade [13,14]. The study was approved by the Bond University Human Research Ethics Committee (approval RO1688B). The initial aim was to recruit 10,000 participants and the goal was two-fold: (1) to document health profiles and injury rates in recreational runners, (2) to discover gene-environment interactions associated with two common types of lower leg injuries in runners—Achilles tendinopathy and bone stress injury. The survey, available online through the SurveyGizmo platform (Boulder, CO, USA) for a period of 25 months, played two roles: (1) to measure self-reported running habits, injury profiles, physical and mental health indicators, and nutrition in recreational runners and (2)

to act as a screening tool by revealing factors for eligibility to the genetic study.

The genetic study involved an email request to eligible participants to confirm their postal address containing an electronic copy of the participant information sheet and consent form. Email respondents were mailed information and consent documents to sign, a saliva collection kit (Oragene DNA Collection Kit, DNA Genotek Inc., Ontario, Canada), instructions for collection, and a reply-paid envelope. The consent form included a request for permission to store the participant's sample in an approved Sports Science & Exercise Biobank specimen repository and shared with other ethically approved research teams. Participants were deemed unreachable when no response was received to the initial email plus 2 reminders, or when their sample was not returned after delivery plus 2 email reminders. A second saliva kit was sent to a small number of those who reported lost or damaged kits.

Participants and Survey

Participants self-selected for inclusion in the survey on the basis of the following criteria: recreational runners aged 18 or older who run more than 15 km per week. Between September 2014 and October 2016, 9069 participants initiated the 30-min Web-based survey and 5248 completed it. Some participants completed the survey 2 times (N=233), some 3 times (N=13), 4 times (N=3), or 5 times (N=1). Only the most recent submission was used for data analysis. Despite the selection criteria, 213 participants reported running less than 15 km per week in the actual survey, but a decision was made to include them in the current analysis.

Eligibility for genetic analysis was complex and participants were not made aware of inclusion criteria so they would not self-deselect from the survey on this account. It included the following: running more than 15 km per week, 18 to 50 years old, having selected the items "Caucasian European" or "Mediterranean" for at least 3 grandparents when asked about their ethnicity, nonsmoker, absence of musculoskeletal comorbidities (arthritis or osteoporosis), medications (quinolone antibiotics, chemotherapy, or others), and recent lower limb fractures. Ethnicity was restricted to simplify genetic association analysis, which in multiethnic cohorts can potentially conceal or confound weak genetic effects [15]. An Australian address was required to eliminate issues with import of biological material. A key requirement for eligibility was acceptance of the following: "I give permission, if I am eligible, to be contacted in the future to provide a saliva sample for genetic related analysis." No individual feedback was promised to participants at any stage of the study.

Procedure

The full panel of recruitment activities used throughout the study is presented in Table 1. To assess if this cohort was representative of the Australian population of runners, the sample was compared with the 2016 AusPlay survey, based on telephonic interviews of a probability-based sample of 70,000 [16]. In January 2016, with only 2232 respondents of the targeted 10,000, a survey item was added asking respondents how they had learned about the study.

Table 1. Summary of the recruitment strategies used for this study including the outcomes obtained other than recruitment. The total cost per strategy and the cost per participant in Australian dollars are estimated.

Strategy, methods, and channels	Outcomes (other than recruitment)	Types of expenses	Estimated cost (Aus $)	Participants (n)	Cost per participant (Aus $)
Facebook					
Group page with regular posts	Page followers and post sharing	N/A[a]	N/A	N/A	N/A
Paid advertisements	N/A	N/A	N/A	N/A	N/A
Posts in other pages	N/A	Advertising fees	1624	979	1.66
Other social media					
Twitter	N/A	N/A	N/A	N/A	N/A
Instagram	N/A	N/A	N/A	N/A	N/A
Newsletters	N/A	None	0	324	0
Web-based media					
Relevant articles	Presence in webpages	N/A	N/A	N/A	N/A
Radio interview	Podcast	N/A	N/A	N/A	N/A
Press interview	Blog post	None	0	161	0
Running events					
Flyers, emails to event participants	N/A	N/A	N/A	N/A	N/A
Presence in race results emails	N/A	N/A	N/A	N/A	N/A
Contact with running-related businesses	Further promotions	Travel	4173	458	9.11
CityFit Expo					
Flyers	N/A	Printed materials, travel, stand booking and fitting	N/A	N/A	N/A
Presence in Expo social media	N/A	Printed materials, travel, stand booking and fitting	N/A	N/A	N/A
Contact with running-related businesses	Further promotions	Printed materials, travel, stand booking and fitting	5249	160	32.81
Parkrun					
Presence at events	N/A	N/A	N/A	N/A	N/A
Newsletters	N/A	N/A	N/A	N/A	N/A
Facebook	N/A	None	0	368	0
Referrals (personal and professional)					
Emails to previous survey participants	Facebook posts	N/A	N/A	N/A	N/A
Sports health professionals	Advice to patients	N/A	N/A	N/A	N/A
Word of mouth	N/A	None	0	144	0
AIS[b]					
Website	N/A	N/A	N/A	N/A	N/A
Social media	N/A	None	0	133	0
Email					
Running events	Mentions in newsletters	N/A	N/A	N/A	N/A
Running clubs	Invitations to events	N/A	N/A	N/A	N/A

Strategy, methods, and channels	Outcomes (other than recruitment)	Types of expenses	Estimated cost (Aus $)	Participants (n)	Cost per participant (Aus $)
Running-related businesses	Facebook, other social media	N/A	N/A	N/A	N/A
Fitness business, personal trainers, running coaches	Referrals	N/A	N/A	N/A	N/A
Triathlon and athletics state organisations	N/A	None	0	Unknown	0
Incentives					
Discount promo codes to participants	N/A	N/A	N/A	N/A	N/A
Competitions	N/A	None	0	Unknown	0
Total			11,046	2760	4

[a]N/A: not applicable.

[b]AIS: Australian Institute of Sport.

The purpose was to monitor the success of each recruitment channel with the goal of optimizing future efforts. Data from the remaining 2776 responses were analyzed based on this item. Finally, the demographic factors associated with participants' willingness to be contacted for genetic research, their actual participation in the research once contacted, and their consent to have their genetic material stored in a biobank were assessed.

Statistical Analyses

Categorical data were arranged in contingency tables and assessed by goodness-of-fit chi-square test in which the expected frequencies (E) were determined from the observed frequencies and tested with the formula $(O-E)^2/E$, except where stated otherwise. The null hypothesis was that the observed frequencies did not differ from the expected frequencies and it was rejected if P value was <.05. Cells for which the standardized residuals had an absolute value higher than 5.00 were considered major contributors to the statistically significant chi-square value and indicated with asterisks. All statistical analyses were conducted using the R statistical software package (R Core Team) [17].

Results

Aim 1: The Recruitment Process

Age, sex, country of citizenship, and weekly running distance are associated with recruitment strategy. Recruitment strategies spanned a number of methods, either paid or free of cost (Table 1). An early partnership with parkrun [18], an organizer of free weekly running events, returned numerous participants through communications in newsletters, presence at events, and parkrun Facebook pages (Figure 1). Direct contact with runners at popular events, competitions for running apparel, and social media presence accounted for peaks in recruitment rates. However, throughout the second half of 2015, participation rates were very low. In 2016, a survey item was added to assess participants' self-reported recruitment channel, and a new recruitment campaign was initiated. New methods that incurred a cost comprised advertising in Facebook and running-related websites, presence at a fitness expo, and presence at 9 running-related events, including 7 races and 2 Running Film Festival premieres. Facebook paid advertising was conducted

with evolving criteria—people interested in running aged 30 to 50 years from February to April and aged 18 to 50 years from May to October. Free strategies comprised the creation of a study Facebook page with regular updates, Web-based media articles and interviews, and agreements with sports-related businesses to provide online discount codes (10%-25% off).

References to incentives were included in the Facebook advertisements (Figure 2). In June 2016, an email campaign contacted all previous respondents (3000 at that stage) requesting help by word of mouth and social media, and hundreds of emails were sent to running event organizers, running clubs, and other running-related businesses. Throughout the recruitment period, the study was supported by the social media, communications, design and commercial capability of the AIS, which provided expertise and some assistance at no cost. The average cost per participant for the period between January and October 2016, excluding the cost of researchers' time, was estimated as Aus $4 (Table 1). The age and sex representativeness of this cohort could be assessed by comparing these data to AusPlay, the national survey of sports participation [16]. The population estimates from AusPlay were used to derive expected values, and the significance of the chi-square test suggests that the sample selected for our study was overrepresented in runners aged 35 years and older and female runners (Table 2). It must be noted, however, that AusPlay reports participation at least once per year in athletics, track and field, which for over 95% of this population involves running and jogging, and our inclusion criteria required regular running.

Facebook recruited the largest number of participants, but it was also the most diverse strategy, comprising paid and free channels such as targeted advertising, our study page, posts on running-related pages, and personal referral. Other strategies contributed directly to recruitment and frequently provided additional outcomes, for example physical presence at events allowed contact with business representatives which led to promo codes or contact with bloggers or journalists which in turn led to interviews and articles. Some of these additional outcomes ultimately returned more participants than a direct contact with runners.

Different recruitment methods delivered different demographic associations (see Multimedia Appendix 1). The standardized residuals of the chi-square statistic suggested a high contribution of 35- to 44-year-old participants to recruitment by Facebook. Older participants were overrepresented when recruitment was mediated by other social media and parkrun, and participants recruited through the AIS tended to be overrepresented in the 18 to 24 age category. Facebook recruitment showed an association with female participation, whereas Web-based media (blogs, podcasts, and newsletters) appeared to recruit more male participants. People whose country of citizenship is not Australia were less likely to be recruited by Web-based media but more easily recruited through direct presence at running events.

Figure 1. Response activity during the recruitment period. The vertical dotted line at the end of Jan 2016 represents the date at which the additional survey item was included to determine the recruitment channel reported by respondents.

Response Activity

	2014			2015													2016								
	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct
Running events																			*		* * *			* * *	* *
Running events (online presence only)																				*	*				*
Incentives																				* *		* * * * * * * * *			
Facebook ads												* * *					* *								
Other ads			*									* * * *					*			* *			
Online media																				* * *	*				*
Parkrun	* * * * * * * *			*													*				*			
Emails to running clubs		* * * * * *														* * * * * * * * * * * * * * * * * * *						
Emails to previous participants																					*				
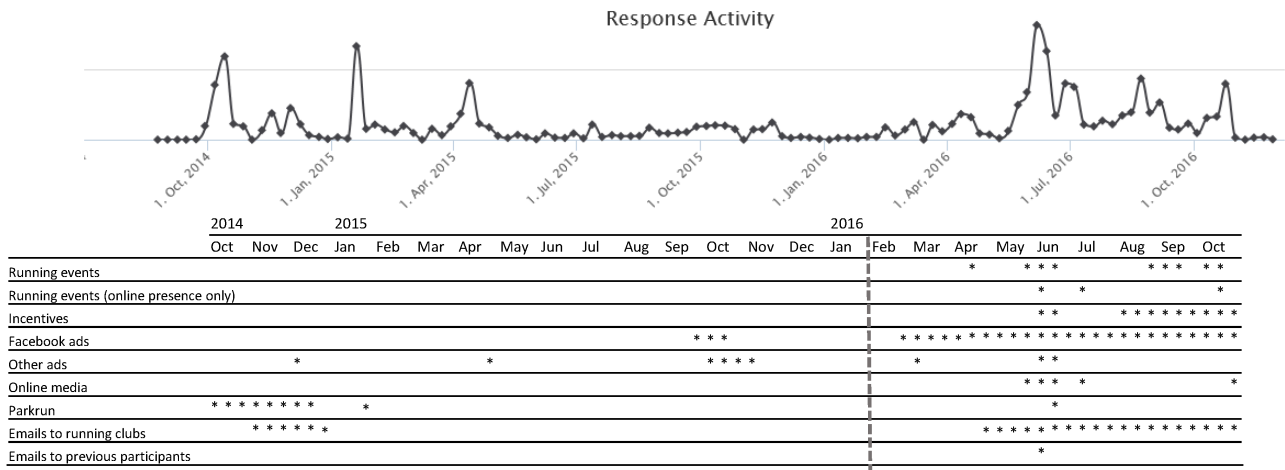
Figure 2. Example of Facebook advertisement including promotional code incentive.
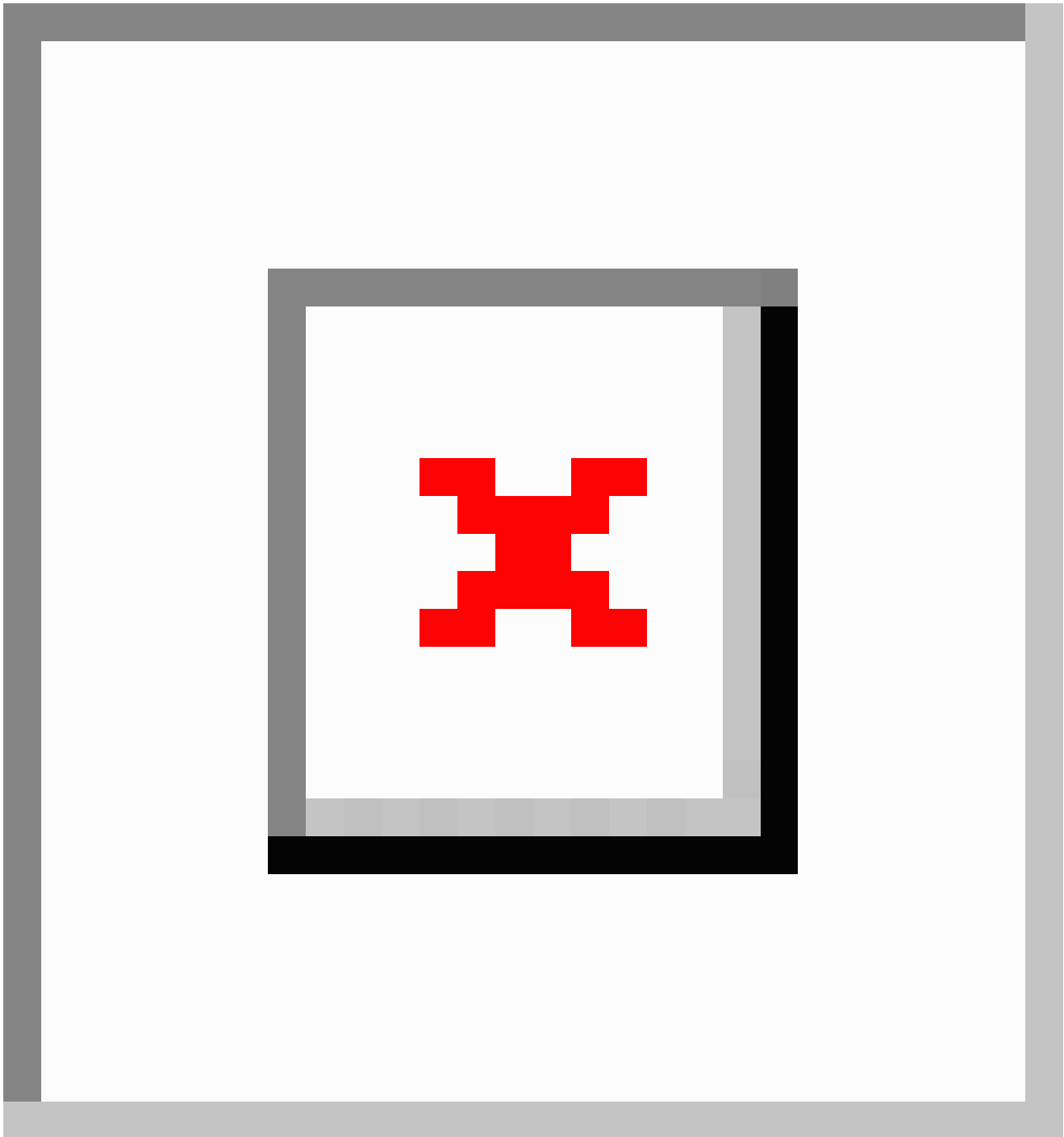
Table 2. Age and sex estimates on athletics, track and field participation from the 2016 AusPlay telephonic survey. Expected values were derived from the AusPlay estimates and tested against observed values.

Age and sex categories	AusPlay survey Estimate (×1000)	This study		Significance
		Expected	Observed	Chi-squared *P* value
Total	2891.3	4976	4976	
Age in years				
18-24	567.9	977	356[a]	
25-34	897.3	1544	1176[a]	
35-44	713.4	1228	1635[a]	
45-54	466.9	804	1226[a]	
55-64	174.5	300	463[a]	
65 and older	71.3	123	120	<.001
Sex				
Male	1618.4	2785	2272[a]	
Female	1273.0	2191	2704[a]	<.001

[a]Cells that are the main contributors to the chi-square test statistic.

Respondents reported their average weekly running distance (see Multimedia Appendix 1), and the chi-square test revealed a significant association between recruitment method and distance covered. The standardized residuals showed that participants who run less than 20 km per week were more highly represented in the Facebook and parkrun categories. In contrast, those who run 40 km per week or more, showed the least presence in the parkrun category. As the study was focused specifically on injury, this factor was also tested for association with recruitment methods. Over half of the participants had sustained an injury in the past 2 years, however this rate was not significantly different between the different recruitment categories. No association was found between ethnic origin or eligibility for genetic analysis and recruitment method. Overall, recruitment methods appear to have affected runners' profiles with regard to age, sex, country of citizenship, and weekly running distance, and the overall sample distribution is dominated by older respondents.

Aim 2: The Genetic Study

Age is associated with respondents' attitudes and actual participation in genetic analysis. Early in the survey, before exposure to demographic questions and after exposure to the participant information sheet, participants had the option to tick a box for each of the following items: "I give permission, if I am eligible, to be contacted in the future for related research" and "I give permission, if I am eligible, to be contacted in the future to provide a saliva sample for genetic-related analysis." Positive answers were given, respectively, by 93.91% (4663/4965) and 89.81% (4459/4965) of participants (Table 3). The chi-square test showed significance for both items, with the 18- to 24-year-old group as the largest contributor to the

former, and both age groups below 35 as key contributors to the latter item. Overall, the rates of positive answers tended to increase steadily with older age, from 75.1% (266/354) to 96.6% (115/119) for willingness to participate in genetic research. The association with sex was weak and potentially confounded by an association between age and sex. Participants were also asked the ethnic group of each of their grandparents because an exclusion criterion for the genetic study was to have less than 3 Caucasian European or Mediterranean grandparents. The results suggest that this majority group was more willing to participate in genetic or other research than the minority group, formed by individuals with 2 or more grandparents of Indigenous Australian or Torres Strait Islander, Polynesian, Asian, African, other, or unknown ethnicity.

A total of 1664 participants met the inclusion criteria for genetic analysis, including consent, ethnicity, and age, and the following results are limited to this cohort (See Multimedia Appendix 2). Eligible participants were contacted by email to request confirmation of contact details. Of all the participants 9 lived overseas, 4 declined participation at this stage, and 278 were deemed unreachable. A total of 1323 out of 1664 (80%) participants replied to emails requesting contact details and 1142 of 1323 (86%) returned saliva samples. Younger age was significantly associated with a lower rate of response to emails requesting contact details, but it did not affect sample return rates. A total of 1038 of 1142 participants (91%) consented for sample storage and biobanking, and no association was observed with age or sex. Overall, no independent association was found between recruitment strategy and follow-up rate, sample return, or biobank consent (results not shown). A graph depicting the rates of participants' loss in the different age brackets throughout the study is shown in Figure 3.

Table 3. Willingness to be contacted for related or genetic research as stated by respondents in the survey, shown by ethnicity, age or sex.

Categories	Total (n=4965)	Permission to be contacted for related research			Permission to be contacted for genetic analysis		
		Yes (n=4663)	No (n=302)	Chi-squared P value	Yes (n=4459)	No (n=506)	Chi-squared P value
Ethnicity, n (%)[a]				<.001			<.001
Caucasian European/ Mediterranean	4508 (87.8)	4255 (94.39)	253 (5.61)		4090 (90.73)	418 (9.27)	
Other	456 (5.0)	410 (89.9)	46 (10.1)[a]		371 (81.4)	85 (18.6)[a]	
Age, n (%)				<.001			<.001
18-24	354 (7.1)	309 (87.3)	45 (12.7)[b]		267 (75.4)	87 (24.6)[b]	
25-34	1173 (23.6)	1076 (91.73)	97 (8.27)		1012 (86.27)	161 (13.73)[b]	
35-44	1632 (32.9)	1554 (95.22)	78 (4.78)		1495 (91.61)	137 (8.39)	
45-54	1225 (24.7)	1165 (95.10)	60 (4.90)		1139 (92.98)	86 (7.02)	
55-64	462 (9.3)	444 (96.1)	18 (3.9)		430 (93.1)	32 (6.9)	
65 and over	119 (2.4)	115 (96.6)	4 (3.4)		116 (97.5)	3 (2.5)	
Sex, n (%)				.499			<.01
Male	2266	2122 (93.65)	144 (6.35)		2063 (91.04)	203 (8.96)	
Female	2699	2541 (94.15)	158 (5.85)		2396 (88.77)	303 (11.23)	

[a]Missing n=1.

[b]Cells that are the main contributors to the chi-square test statistic.

Figure 3. Percentage response decline throughout the genetic arm of the study, from eligibility (including stated willingness to participate) to reply to email requesting contact details ("Replied"), sample return by mail ("Returned") and biobank consent, categorised by age groups. The most significant decline was seen in the reply rate of the 18-24 year old participants.
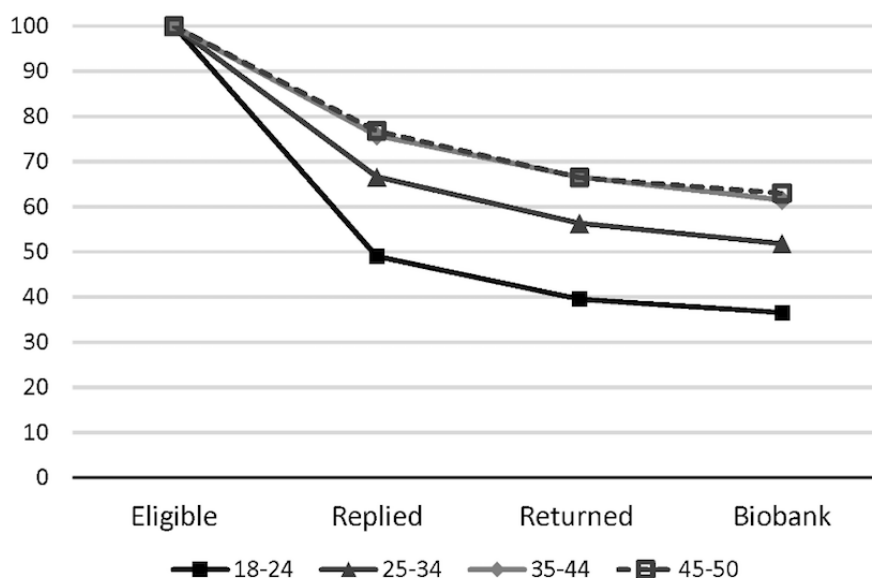
Discussion

Part 1: The Recruitment Process

Web-based health data collection is now possible because of the ubiquitous presence of the internet and the multiplicity of access devices. In addition, technologies for the collection of saliva samples without a skilled practitioner or refrigeration in transit facilitate remote donations for genetic analysis. These

two advances enabled the design of an epidemiological and genetic study with the ambition of recruiting 10,000 survey participants and obtain at least 3000 genetic samples [14]. The final numbers, however, amounted to slightly under 5000 participants and 1142 samples in a period of 2 years [13]. This sample size leaves the genetic study underpowered, but with potential to contribute to meta-analyses and replication studies. The number of adult runners in Australia in 2015-2016 was estimated over 2.8 million [16], so there was no shortage of

potential participants. Here we analyzed the recruitment strategies employed, their efficiency, and their impact on population representativeness. We also searched for associations between participants' characteristics, recruitment, and retention throughout the genetic arm of the study.

Every recruitment method shows potential for bias [19], so to minimize overall bias we used a combination of recruitment strategies. Nevertheless, a comparison with data from the randomly sampled AusPlay sport participation survey [16] revealed a significant underrepresentation of young adults. It must be noted that the analysis of recruitment strategies presented here is based on data obtained in the second wave of recruitment, after an item addressing the source of recruitment was included in the survey, and provides no information on recruitment trends in the initial wave of recruitment. Despite social media being considered as a suitable platform for this population [20] and Facebook being the most popular social media platform in Australia for all ages [21], neither Facebook nor other social media boosted the participation of younger adults in our study. Facebook preferentially recruited participants in the 35 to 44 years age bracket, which may be a result of our advertising campaign being targeted to runners aged 30 to 50 years during the first 3 months, before it was extended to ages 18 to 50 years for another 6 months. However, targeted advertising was only one of the many Facebook-related strategies used to promote the study, in addition to snow-balling, presence on pages for running groups, and others. It is possible that physically active young adults are just difficult to reach, and use of Facebook is not sufficient to promote a research study to this population. Alternative channels such as universities or sports organizations may have been more successful. In fact, our own website, the AIS, which provides programs and facilities for elite athletes, was the only channel that recruited a representative proportion of young adults. Conversely, a network of free, weekly, timed 5 km outdoor runs called parkrun recruited numerous participants, but a high proportion of those were in the 55 to 64 years age category. Overall, the reported bias in age distribution for each recruitment method highlights the need to use a range of recruitment activities. One cannot expect, however, that a mix of methods will cancel bias, as is the case with this study where the most successful strategies returned samples biased toward older ages.

Other associations were evident. Sex distribution was affected by Facebook and Web-based media. Despite an absence of sex-related differences in social media or Facebook usage or behavior [21], the female recruitment rate through Facebook of 61.4% (601/979) was high, in line with previous studies that also used Facebook (60% in average) [5]. The large contribution of the Facebook cohort to the sample may have been responsible for the overall female predominance in the study, although it is not unusual for women to show higher rates of enrollment in health research studies [22]. Respondents who run less than 20 km per week were overrepresented and those who run over 40 km per week were underrepresented in the parkrun group, which aligns with the observation that parkrun attracts people with lower running ability [23].

Overall, no specific strategy combined the desired requirements for high recruitment rate, population representativeness, and

low cost; however the relative representation reported here could help researchers choose the recruitment methods that best fit their target population. Additionally, it is recommended that an item asking for participants' self-reported method of recruitment is included in surveys so that these data can be used to assess or modify recruitment strategies. This study was characterized by two waves of intensified recruitment, one at study roll-out and another after a long lag in recruitment. Each wave involved consultation with the AIS communications team and the design of a tailored recruitment plan. The initial campaign was successful but it lacked momentum, and another campaign, reported here in detail, was required to boost recruitment. Despite the assistance of communication experts and the use of a reputable and popular brand such as the AIS, the study only recruited half of its projected participants. According to our experience, large-scale recruitment for internet data collection sits at the interface of marketing and research and acts in a direct competition with many other scientific studies and market research. In this competitive environment, the communication requirements for large-scale recruitment are beyond the researchers' expertise. Only by engaging marketing experts and allocating sufficient resources will a study succeed in large-scale recruiting.

Part 2: Respondent Participation in the Genetic Study

Significant time and consideration was invested in developing a process of informed consent that explained the study's purpose in a clear and simple way. The participant information sheet was followed by requests for permission to be contacted for related research and for genetic analysis. The fact that the former question, open and nonspecific, received a slightly higher positive answer rate than the latter, which is linked to this specific research study and backed by detailed information, aligns with reports indicating that the presence of a genetic component in studies aimed at the general population has a negative impact on survey participation [10,24-26]. Overall, willingness to participate in the genetic arm of the study was slightly higher than in other studies (90% vs 83-86%) [10,26,27]. As shown by others, younger age was associated with a negative answer to both requests [11,26,27]. This could be linked to lower levels of trust in research and greater privacy concerns in younger adults [11,26,28], and a more altruistic attitude to research in older adults [29]. Those who were not Caucasian European or Mediterranean were significantly more likely to answer negatively despite the survey item for ethnicity being located well after the request for permission to be contacted. This agrees with some studies examining the willingness of ethnic minorities to participate in genetic research [3,22,26] but not with others [4,27]. It must be noted that all these studies were conducted in the United States and the minorities described were African American and Hispanic, whereas our study was conducted in Australia and the minorities encountered were primarily Asian, Indigenous Australian, Pacific Islander, and African. The combined observations indicate that there is a broader pattern suggesting that recruitment should be tailored to enhance representation of ethnic minorities in genetic studies.

Only 80% of eligible, willing participants responded to the follow-up email, similarly to previous genetic research studies [3,4]. We can only speculate about the reasons for this drop. As

people's belief in the importance of genetic research appears to be higher than their individual willingness to participate [8], it is likely that participants only considered their individual concerns when confronted with actual participation. Alternatively, email, the vehicle of contact, is prone to loss by incorrect records or spam filters, or it may simply be ignored. Accordingly, the fact that response rates approached 65% in the 18 to 24 years age category versus 83% in the 35 to 50 years age category may reflect the abovementioned association between age and attitude to research or privacy, or it could reveal age-related differences in email usage. Previously reported age effects in studies that did not involve email [3], combined with recent data supporting that email is still strong in young adults [30], seem to indicate that the effect stems from different attitudes to research or privacy. We recommend that studies targeting young adults design contact protocols that match the specific attitudes supported by this population.

An additional drop in retention occurred when participants were mailed the materials needed to donate their sample. Despite the simple procedure designed to minimize participant burden, only 86% of the samples were returned. However others have reported lower saliva kit return rates between 42% and 82% [2,3,31,32]. Unlike another study [3], no age associations were found at this stage, although the older age categories tended to show higher return rates. This was the most expensive drop in participation because it combined administrative costs, postal fees, and the cost of the collection kits. Informal feedback from participants indicated that they might have been more engaged had they been given a deadline for sample return. A study in young adults (age around 28 years) found that offering a small incentive for sample collection tripled the odds of obtaining a sample but decreased the likelihood of obtaining biobank consent [4]. These strategies were not tested by us but may be worth considering. Of those respondents who returned the saliva sample, 93% gave consent for biobank storage, irrespective of age or sex. This rate reveals that, once enrolled in the study and having donated a sample, participants generally see the benefits of storage and sharing their deidentified sample for future studies.

Overall, this analysis reveals an age-related bias experienced throughout the study. Sex was associated with survey participation but not with other steps of the process, in agreement with some studies [27] but not with others [3,22,33]. Our sample comprised physically active people and participation rates suggest that they are at least equivalent to other populations

in their likelihood to participate in genetics research. There are two previous studies providing evidence for [3] or against [22] an association between physical activity, or exercise capacity, and participation in genetics studies in participants aged 40 years or older. Nonetheless, to our knowledge, no studies to date have examined this kind of association in younger cohorts, and our data may suggest that physically active people aged under 35 years are particularly hard to reach and retain for genetics research. Therefore, it is recommended that studies targeted at this population use recruitment strategies designed to match the specific characteristics of this population.

This study is not without limitations. It is an observational study that lacks a systematic assessment of confounding factors. Recruitment strategies were self-reported, and our measure of recruitment strategies from the participants' response to the survey item is a gross measure. In addition, some recruitment channels, such as promotions and the email campaign to previous respondents, could not be assessed for success because these items were not included in this survey item. This item was added to the survey over halfway through the recruitment period, precluding any analysis on the initial phase of recruitment. The target population for Facebook advertising, a successful recruitment channel in this study, was also updated halfway through the campaign. This adaptive move, which aided with recruitment to satisfy the primary aims of the study, imposes an additional limitation to the current analysis. A limitation to the generalizability of the results is the inclusion or exclusion criteria of both the survey-based and genetic arms of the study.

Conclusions

The internet undoubtedly offers many opportunities to reach potential participants for genetic research. However, the results of this study show that initial contact and follow-up methods need to be designed according to the target population. A caveat of these studies is that, even though initial recruitment is done through popular channels such as social media, subsequent contact needs to be done in person or by mail, which exposes these studies to the traditional hurdles such as email or parcel loss, change of address or loss of participants' interest due to lack of immediacy. Contact by email could be replaced by more immediate channels such as text message or social media; however, the requirement for a mailing address for parcel delivery will continue to be a challenge for recruitment, and it is difficult to conceive a system that would eliminate this challenge.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Respondents' characteristics by recruitment strategy. Superscript "a" indicates cells that are the main contributors to the chi-square test statistic.

[XLSX File (Microsoft Excel File), 15KB - resprot_v7i5e141_app1.xlsx]

Multimedia Appendix 2

Participants who replied to contact emails for the genetic arm of the study, those who returned the sample and those who provided signed consent to biobank their sample, calculated as percentages of the previous category and categorized by age and sex. Superscript "a" indicates cells that are the main contributors to the $\chi 2$ test statistic.

[XLSX File (Microsoft Excel File), 12KB - resprot_v7i5e141_app2.xlsx]

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Abbreviations

AIS: Australian Institute of Sport

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<u>Corrigenda and Addenda</u>

Expression of Editorial Concern, Correction of Conflict of Interest and Affiliation

JMIR Editorial Office

Expression of Editorial Concern

We are hereby expressing serious concerns over conflicts of interests (COI) by the authors of a JMIR Research Protocols paper [1] as well as a subsequent JMIR Public Health & Surveillance [2] paper (where the results of the protocol were published). While we think that complementary medicine (as well as associated lifestyle changes, technologies promoting such lifestyle changes, and other tools and behavioral innovations covered by JMIR journals) deserve to be evaluated in a scientific and evidence-based manner, it is important that these evaluations are performed either by independent researchers who do not have a stake in the outcome, or—if factors exist that could be perceived as conflict of interest—any such potential conflicts of interests are fully disclosed and properly managed from the outset (such as data vetting by an independent party). In the case of these two papers, the initial disclosure was incomplete, and it is unclear to what degree the competing interests of the authors were properly managed when the research was conducted.

In the JMIR Research Protocols [1], and subsequent results paper [2], authors describe a comparative analysis comparing a group of people associated with a specific "complementary medicine health care organization" (Universal Medicine, UM), with the general population, concluding in their results paper that the UM group has "unusual health indicators" (more favorable than the general population).

Both submitted manuscripts originally contained conflict of interest (COI) statements which read as follows:

> CS and VM are insiders in that they attend Universal Medicine events. However, they have received no funding, reimbursement, or other consideration from UM or its stakeholders, and no instructions or directions of any kind from UM or its stakeholders. No other competing interests exist.

After acceptance, our freelance copyeditor edited this statement out and replaced it with our standard verbiage "Conflicts of Interest: None Declared," which is used when there is no COI, because "attending events" in itself is not normally something

that would be considered a conflict of interest requiring disclosure. Authors did not object to these copyediting changes and approved the galley proofs. Their signed "license to publish" does not contain any further COI disclosures.

Shortly after publication, we received a 12-page letter from a third party whistleblower, detailing extensive undisclosed conflicts of interests of the authors, which made clear that their COIs go way beyond being "insiders in attending Universal Medicine events." The letter was also addressed to another journal which published another protocol of the group [3], as well as to the University of Queensland (the lead author CS is associated with that university in his capacity as a PhD student).

We asked authors to provide a more detailed conflict of interest statement for a possible correction of the original papers.

In response, the lead author submitted a 1-page revised COI statement (see below) detailing that all four authors have varying degrees of association with Universal Medicine and are—most significantly—members of the "Practitioners' Association" which is the body regulating practitioners who are "qualified to practice Universal Medicine modalities." Of special significance is that two authors have "occasionally offered paid private healing sessions."

The revised COI by the author also claims that "all authors have experienced substantial health benefits since they started visiting UM events." In addition, they all have published blogs on UM associated websites. The wife of the lead author is—according to the revised COI—involved in "voluntary activities around producing content" for a UM-associated company and is a "company secretary" of the UM-associated company Unimed Living (owned through another company by the UM-founder Serge Benhayon) and "does this in an honorary capacity. She is not a director or shareholder" and "does not receive any financial incentives" from UM.

We consulted the original peer-reviewers of the results paper showing them the updated COI and they stated they would not have accepted the manuscript would they have known about these extensive COIs.

We suggested to the authors that we feel that given the significant COIs (as well as the statistical errors in the results

paper, which inflated the effect sizes) both articles should be retracted and we would prefer to do this with their consent. The lead author rejected this with the argument that they originally submitted a conflict of interest which the journal removed. We maintain that the original COI submitted stating that two authors "attend UM events" was inadequate and unclear, and did not cover the full extent of the COI. The lead author CS also maintains that the involvement of his wife as company secretary for a Universal Medicine company is irrelevant because it is not a paid position. We checked the company registration documents of Unimed Living and CS's spouse is indeed listed as company secretary, which is considered an "officer" of a corporation in Australia, so this is not just a merely administrative position, rather, they have many of the same duties and obligations as directors [4]. Thus—even in the absence of remuneration—such involvement constitutes a significant COI.

We remind our authors of the fact that "The potential for conflict of interest can exist whether or not an individual believes that the relationship affects his or her scientific judgment." [5] and that—while financial relationships are the easiest to identify—conflicts can occur for other reasons, such as religious beliefs, personal relationships, and intellectual passion.

Our concerns with the COI of the lead author (and his spouse) go beyond financial COIs, as in his blog the lead author describes how meeting the UM founder "changed our lives profoundly" [6], and his spouse is describing "seemingly miraculous changes" [7] as a result of UM. This level of "passion" for UM and their involvement may affect the authors' scientific judgement.

The University of Queensland has launched an investigation, but the investigation is (as of May 11th, 2018) not complete. In the meantime, we are publishing the updated COI statement as corrigendum and this statement of editorial concern, while we await the outcome of the university investigation to decide on further steps.

We are furthermore concerned about the fact that the authors recently also requested the removal of the University of Birmingham as affiliation of one co-author (JK), which is a unusual request.

While authors never claim otherwise, we should stress that the proposed [1] and executed research [2] does not provide any evidence that any Universal Medicine modalities are effective in making people healthier. There are severe limitations regarding on what can be concluded from an observational, cross-sectional study without a control group. One possible explanation for why UM members are apparently healthier than the rest of the population is simply selection bias, meaning that people being associated with UM were always healthier, or less healthy when they joined UM, with "regression to the mean" over time. Another possible explanation involves confounding factors, or the simple fact that UM members adopt healthier lifestyles.

G. Eysenbach

Editorial Director, JMIR Publications

Authors' Corrigendum

(as submitted by the authors)

Affiliation

The authors request to change Jane Keep's affiliation to:

> The Leaders Leader, Greater London, United Kingdom

Instead of:

> Health Services Management Centre, School of Social Policy, University of Birmingham, Birmingham, United Kingdom

Conflicts of Interest

The authors were advised to change the conflict of interest statement. The new Conflict of Interest Statement should read as follows:

> All four authors have varying degrees of association with Universal Medicine and are currently members of the Esoteric Practitioners' Association (EPA) which is the body regulating practitioners who are qualified to practice Universal Medicine modalities.

> Universal Medicine has a focus on complementary-to-medicine practices, that aim to support and augment medical treatments.

> Jane Keep has attended Universal Medicine workshops since October 2003. Jane Keep was a director of Universal Medicine UK until 2013. She is a member of the EPA, and a committee member of the EPA, and has been accredited by the EPA to offer Esoteric Healing Modalities since 2010. From 2009-2012 Jane ran a small clinic in England which offered Universal Medicine healing modalities. Since 2012 Jane has been working in corporates/universities/hospitals and occasionally offered paid private Esoteric Healing sessions, though since 2014 she has offered no paid private Esoteric Healing sessions. She was a contributor to Unimed Living 2013 – 2016. Jane has a PhD which referenced the work of over 300 people including Serge Benhayon.

> Eunice Minford is a Consultant General Surgeon, and has trained as an Interfaith Minister and Spiritual Counsellor. She also attended the National University of Ireland and obtained a degree of "Master of Applied Christian Spirituality" studying Sacred Esoteric Healing in her thesis. Eunice is also editor of the website "Medicine and Serge Benhayon" and a contributor to that website and to the "Unimed Living" website. She has her own blog "The Soulful Doctor" where she discusses, et al, Universal Medicine. She is also on the EPA professional committee as well as a medical advisor to, and the International Patron of, the EPA. She is a trained esoteric healing practitioner and provides occasional private sessions.

Christoph Schnelle is a financial adviser and has some Universal Medicine associated persons among his client base. Christoph is currently working towards his PhD with The University of Queensland, the subject of which is two randomised controlled trials of Esoteric Connective Tissue Therapy (a Universal Medicine modality) on chronic low back pain and has accumulated case studies as part of this project. Christoph Schnelle's wife, Nicola Lessing, is involved in voluntary activities around producing content for "Unimed Living" and other websites. Nicola is company secretary of Unimed Living and does this in an honorary capacity. She is not a director or shareholder of Unimed Living. She is not employed by Universal Medicine or Unimed Living and does not receive any financial incentives from Universal Medicine or Unimed Living.

Vanessa McHardy is involved in voluntary activities around producing content for "Unimed Living", presenting at a conference on Psychological Well Being in 2013 on the Gold Coast of Australia. She has no other involvement other than what is set out below.

All four authors have experienced substantial health benefits since they started visiting Universal Medicine events. They all have published blogs on Universal Medicine associated websites and all four have commented on other blogs published on those websites.

All four have no financial ties and have received no money from Universal Medicine or its related entities including no reimbursements of expenses. Each one attends more than 10 Universal Medicine events a year and regularly receive treatments from Universal Medicine accredited practitioners.

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a link to the original publication on http://www.researchprotocols.org, as well as this copyright and license information must be included.

Protocol

Exploring the Waveform Characteristics of Tidal Breathing Carbon Dioxide, Measured Using the N-Tidal C Device in Different Breathing Conditions (The General Breathing Record Study): Protocol for an Observational, Longitudinal Study

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Abstract

Background: In an increasingly comorbid population, there are significant challenges to diagnosing the cause of breathlessness, and once diagnosed, considerable difficulty in detecting deterioration early enough to provide effective intervention. The burden of the breathless patient on the health care economy is substantial, with asthma, chronic heart failure, and pneumonia affecting over 6 million people in the United Kingdom alone. Furthermore, these patients often have more than one contributory factor to their breathlessness symptoms, with conditions such as dysfunctional breathing pattern disorders—an under-recognized component. Current methods of diagnosing and monitoring breathless conditions can be extensive and difficult to perform. As a consequence, home monitoring is poorly complied with. In contrast, capnography (the measurement of tidal breath carbon dioxide) is performed during normal breathing. There is a need for a simple, easy-to-use, personal device that can aid in the diagnosis and monitoring of respiratory and cardiac causes of breathlessness.

Objective: The aim of this study was to explore the use of a new, handheld capnometer (called the N-Tidal C) in different conditions that cause breathlessness. We will study whether the tidal breath carbon dioxide ($TBCO_2$) waveform, as measured by the N-Tidal C, has different characteristics in a range of respiratory and cardiac conditions.

Methods: We will perform a longitudinal, observational study of the $TBCO_2$ waveform (capnogram) as measured by the N-Tidal C capnometer. Participants with a confirmed diagnosis of asthma, breathing pattern disorders, chronic heart failure, motor neurone disease, pneumonia, as well as volunteers with no history of lung disease will be asked to provide twice daily, 75-second $TBCO_2$ collection via the N-Tidal C device for 6 months duration. The collated capnograms will be correlated with the underlying diagnosis and disease state (stable or exacerbation) to determine if there are different $TBCO_2$ characteristics that can distinguish different respiratory and cardiac causes of breathlessness.

Results: This study's recruitment is ongoing. It is anticipated that the results will be available in late 2018.

Conclusions: The General Breathing Record Study will provide an evaluation of the use of capnography as a diagnostic and home-monitoring tool for various diseases.

Registered Report Identifier: RR1-10.2196/9767

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Introduction

Burden of Breathlessness

Respiratory and cardiac diseases that cause breathlessness are both highly prevalent and major causes of health care utilization across the United Kingdom. Asthma is estimated to affect over 3.5 million people, with 250,000 experiencing severe disease with frequent exacerbations [1]. Heart failure (HF) affects over half a million people, while every year up to 1% of the adult population will suffer from a community-acquired pneumonia [2,3]. Many of these patient groups experience comorbid breathlessness such as breathing pattern disorders (BPD) [4]. The combined burden of these breathless patients on the National Health Service (NHS) is enormous, accounting directly for over £2 billion, with an indirect societal cost (time off work and lost productivity) in excess of £6 billion [5-7]. The prevalence of these diseases is increasing [8,9], and it is often becoming difficult for the clinician to diagnose the cause of a person's breathlessness and, once diagnosed, considerably difficult for the person to monitor their own disease effectively [10]. Furthermore, patients who are at risk of hypercapnic failure (eg, progressive motor neurone disease, MND) often find it difficult to identify when their condition is deteriorating and when they require more intensive support. The need for noninvasive ventilation in these patients is often only recognized when they are very ill and leads to an increased length of stay in hospital and poorer patient outcomes [11].

Diagnostic Challenge

Current methods of diagnosing the cause of a person's breathlessness rely on a combination of symptom history and extensive investigations such as spirometry, peak expiratory flow rates, transthoracic echocardiography, blood tests, and radiology. These can be invasive or are effort or technique dependent, making them difficult to perform and often hard to interpret. Many of these conditions lack a personal monitor that can be used by patients at home, making it hard for patients to self-monitor and engage with their management, resulting in poor medicine adherence [12]. There is a need for a simple, effort-independent tool that can aid the clinician in determining a diagnosis and aid the patient in monitoring their condition. A prompt diagnosis allows timely treatment, and accurately identifying when action needs to be taken empowers the patient and ultimately could improve outcomes.

Capnography

Capnometers graphically measure carbon dioxide (CO_2) in exhaled breath and provide clinicians with a noninvasive measure of systemic metabolism, circulation, and ventilation. Capnometers have been a standard of care in general anesthesia for over 30 years and are also widely used in critically unwell patients [13]. Their use is now even recommended to assess adequate cardiopulmonary resuscitation in hospital cardiac arrests [14,15]. However, use is currently limited to these specialist hospital areas in part because of the high cost of capnometers and the requirement for integrated information systems by which data are displayed.

The Cambridge Respiratory Innovations Limited "N-Tidal C" Capnometer

Cambridge Respiratory Innovations Limited (CRiL), a UK-based company, has developed a novel infrared III-V light-emitting diode capnometer that is intended for use by patients at home to monitor their breathing condition. The N-Tidal C data collector device is a class 1, Conformité Européene marked, handheld device that measures the amount of CO_2 in the user's breath during normal tidal breathing.

The device consists of the main unit and a disposable mouthpiece. The device takes approximately 2 min to self-calibrate. The patient then breathes normally through the mouthpiece until the device gives an auditory and visual signal that the reading is complete (75 seconds). The device records the full dataset of exhaled CO_2 for the duration of use, and the data can be downloaded periodically. Data are analyzed using algorithms developed by CRiL to produce waveforms and can be viewed graphically. It has already been successfully used in a longitudinal clinical study with 30 chronic obstructive pulmonary disease (COPD) patients. This has resulted in the collection of over 2600 75-second breath records containing over 50,000 individual $TBCO_2$ waveforms. This research demonstrated a clear differentiation in $TBCO_2$ waveforms between stable COPD and during a COPD exacerbation [16]. It has also identified the early changes to $TBCO_2$ waveform, indicating an ability to predict COPD exacerbations [16].

We aim to establish a substantial $TBCO_2$ waveform database in multiple different conditions that cause breathlessness. This study will determine whether this form of capnography can be used as a tool for diagnosis of various respiratory and cardiac conditions by comparing waveforms in different medical conditions with healthy controls. It will also provide longitudinal information in specific patient groups with chronic disease. This will identify whether this use of capnography, as recorded by the N-tidal C device, can be used as a self-monitoring tool by patients at home.

Aims and Objectives

Coprimary Objectives

The coprimary objectives of this study are to explore the characteristics of the $TBCO_2$ waveform, as recorded by the N-tidal C device, which can differentiate between different respiratory and cardiac conditions, and to establish a $TBCO_2$ profile for healthy controls.

Secondary Objectives

The secondary objectives for this study are as follows:

- To identify within-patient changes in the $TBCO_2$ waveform that may predict or detect a deterioration of the underlying disease.
- To establish whether the characteristics of any waveform changes before a clinical deterioration are similar in all patients in the same group.
- To identify waveform features that may help inform a larger disease-specific prospective study in the future.
- To describe the relationship between characteristics of the $TBCO_2$ waveform and severity of the primary condition of interest (as measured by disease-specific clinical parameters and symptom questionnaires).
- To compare the use of the $TBCO_2$ waveform (and the N-Tidal C device) in monitoring different breathing conditions with traditional methods of monitoring disease control.
- To monitor the safety of the device in regular use by participants over a 6-month period.
- To establish the *ease of use* of capnography measurement as a potential method of disease diagnosis and monitoring in all participants.
- To identify the ranges of $TBCO_2$ waveform parameter values (minimum and maximum) for the different disease cohorts.

Methods

Overview

A longitudinal, observational study of several cohorts of patients with different medical conditions that result in breathlessness.

Outcome Measures

Primary Outcome

For all conditions, the primary outcome of interest is the twice daily $TBCO_2$ waveform as recorded by the N-Tidal C device.

Safety Outcomes

Any adverse events (AEs) reported during performing the study procedures and any adverse device effects will be recorded.

Patient or Health Care Professional Experience Outcomes

A visual analog scale questionnaire to record the *ease of use* and acceptability of the N-Tidal C device to participants and

health care professionals will be used at the completion of the study.

Study Participants

Participants will be drawn from a range of clinical conditions affecting adults that have symptoms of breathlessness.

Eligibility Criteria

There are overarching eligibility criteria for all clinical populations, in addition to specific eligibility criteria, detailed below for each clinical population, to ensure that the condition of interest is clearly defined and that the participants will be able to complete the study. These are shown in Textboxes 1 and 2.

Additional condition-specific inclusion criteria (definition of required medical condition) are detailed below.

Asthma

Inclusion Criteria

The inclusion criteria was as follows:

1. A confirmed clinical diagnosis of asthma for $\geq$ 6months supported by evidence of *any* of the following:
   a. Airflow variability, with a variability in forced expiratory volume in one second (FEV_1) of >20%, with concomitant evidence of airflow obstruction (FEV_1/ forced vital capacity ratio <70% on spirometry) recorded at any time;
   b. Airway reversibility with an improvement in FEV_1 by $\geq$12% or 200 ml after inhalation of 400 µg of salbutamol via a metered dose inhaler and spacer within the preceding 12 months;
   c. Airway hyperresponsiveness demonstrated by Methacholine (or similar) challenge testing with a provocative concentration of Methacholine required to cause a 20% reduction in FEV_1(PC20) of $\leq$8 mg/ml or equivalent test.

2. Moderate to severe asthma defined as British Thoracic Society stage 3 to 5
3. Exacerbation free for >2 weeks (defined as no increased dose or course of oral corticosteroids or antibiotics)
4. Two or more exacerbations in the previous 12 months with at least one exacerbation within the last 6 months.

Textbox 1. Overarching inclusion criteria.

- Male or female, aged $\geq$16 years
- Willing and able to provide written informed consent

Textbox 2. Overarching exclusion criteria.

- Known other lung, chest wall, neuromuscular, cardiac, or other comorbidity or abnormality that would affect spirometry or other measures of lung function or tidal breath carbon dioxide ($TBCO_2$) measurements
- In the opinion of the clinical investigator, the participant would have difficulty completing the study procedures consistently over the course of 6 months

Breathing Pattern Disorders

Inclusion Criteria

Each participant recruited must have a clinical diagnosis of a BPD by a specialist respiratory physiotherapist.

Chronic Heart Failure

Inclusion Criteria

Each participant recruited must meet the following inclusion criteria:

1. A confirmed clinical diagnosis of chronic HF with both of the following:
   a. A left ventricular ejection fraction <40% on most recent imaging within the last 12 months.
   b. New York Heart Association class 2 to 4
2. Either (i) admitted with an acute decompensation of their HF to hospital requiring intravenous diuretics or an increase in diuretic dose from baseline (eg, 40 mg or more furosemide) within the last 6 months or (ii) stable outpatient with N-terminal pro b-type natriuretic peptide (NT-proBNP) >400 ng/mL in sinus rhythm or NT-proBNP >1000 ng/mL in atrial fibrillation.

Motor Neurone Disease

Inclusion Criteria

Each participant recruited must have a confirmed clinical diagnosis of motor neurone disease.

Pneumonia

Inclusion Criteria

Each participant recruited must have a confirmed clinical diagnosis of pneumonia supported by evidence of consolidation on a chest X-ray or computed tomography imaging.

Healthy Volunteers

Inclusion Criteria

The inclusion criteria was as follows:

1. No known history of lung, cardiac, or neuromuscular disease (defined as no current clinical diagnosis of, or be receiving treatment for, a lung, cardiac, or neuromuscular disease)
2. Body mass index ≤40
3. Nonsmoker, or ex-smoker with ≤ 5 pack year history

Sampling and Sample Size

As this is an observational, proof-of-concept study, there is no formal statistical justification of the sample size, as the purpose of this planned investigation is to gather data on $TBCO_2$ waveform using the N-Tidal C device. If 70 participants use the device 2 times daily over a period of 6 months, the database should include up to 25,000 detailed 75-second respiration records, which will allow time series analysis, comparisons, and correlation with other measures of disease monitoring. This study has been funded by a competitive grant awarded by Innovate UK, and the number of participants recruited into each patient cohort has been restricted by the number of available devices built by CRiL based on the amount of grant funding.

Study Procedures

Recruitment

This study will be conducted at Queen Alexandra Hospital, Portsmouth. Identification of potential participants will be performed in outpatient clinics, inpatient wards, and specialist secondary care clinics in the community depending on the disease cohort. Furthermore, potential participants will also be invited to attend patient information events about the study. These events will be held over 2 hours and introduce the study to potential asthma, BPD, and HF participants identified from clinic lists. At these events, all participants will be given a Participant Information Sheet (PIS), be introduced to the device, and allowed to ask any questions. If interested in the study, they will be given an appointment with the study team for a mutually convenient screening visit. Participants will also be identified at respiratory outpatient clinics and specialist respiratory clinics in the community. In these settings, they will be given PIS and an introduction to the study (verbal and written letter). Potential HF and pneumonia participants will be identified from inpatient wards and outpatient HF services, approached, and given a verbal and written introduction to the study, along with a PIS by a member of the research team. Healthy volunteers will be recruited from hospital staff, with an email sent to all staff (through the research communications team) advertising the study. Potential volunteers will be asked to call or email the study team so that further information (PIS) can be sent via email and an appointment arranged to discuss the study further.

Screening and Enrollment

Patients who express an interest and give informed consent will be screened for the study at an assessment visit at a convenient date and time. Participants identified at the patient information events will be given an appointment with the study team at the event. Participants who are inpatients will undertake their first assessment after they have provided informed consent—as an inpatient and before discharge from hospital. Healthy volunteers will be invited to an initial assessment visit at a mutually convenient time.

Study Assessments

Schedule

The N-Tidal C capnometer will be explained to the patients, and they will be trained how to use it. Patients will be asked to use the device at home over a period of 6 months for the asthma, BPD, HF, MND, and healthy control cohorts and a period of 2 months for the pneumonia cohort. Participants will be asked to use the device at home 2 times per day (morning and evening), or up to 6 times per day if they feel that they are starting an exacerbation or deterioration of their condition. Hospitalized inpatients will also use the device 2 times per day as inpatients and will then continue with the monitoring after discharge from hospital. All patients will have a clinical examination and medical history recorded appropriate to their condition.

Additional disease-specific data such as lung or cardiac function tests will be collected at baseline, 2, 4, and 6 months and at

point of exacerbation, depending on the underlying condition. The outline of assessments at each visit is detailed in Multimedia Appendix 1

Home monitoring will commence as soon as the screening assessments are complete for patients who are recruited from outpatient clinics or specialist secondary clinics in the community. They will commence the day after discharge from hospital for patients who are recruited as inpatients. Home monitoring will include daily N-Tidal C use and three weekly symptom reporting:

1. N-Tidal C: patients will use the N-Tidal C, 2 times daily (morning and evening), and up to 6 times daily if the patient feels unwell or has a deterioration of their disease throughout the home monitoring period until the final outpatient clinic visit.

2. Symptom reporting: asthma, HF, BPD, and healthy volunteer participants will have their disease specific symptoms recorded 3 times a week via an automated telephone service provided by a company called "Message Dynamics." This service has already been used and accepted by patients in previous trials and uses participants' responses to preset questions to evaluate their state of health [17]. The participants will record their symptoms by responding to a series of questions using the telephone keypad. Using the responses recorded, Message Dynamics will automatically alert the study team if a participant's state of health has deteriorated beyond a given threshold. This will prompt a telephone call from a member of the study team to the participant to assess their condition and, if needed, arrange a clinical review to diagnose an exacerbation. If the participant does not answer the initial automated telephone call, there will be no more than two follow-up calls (a maximum of three in total).

At each study assessment, the use of the N-Tidal C device will be reviewed. The study nurse will check that the patient is using the device correctly and will provide additional training if needed. The $TBCO_2$ waveform data will be downloaded from the device, and the study nurse will confirm that the mouthpieces have been appropriately replaced at the required time intervals

Any AEs and any adverse device effects will be recorded. If the patient feels that their condition is deteriorating and or they are experiencing an exacerbation at any point throughout the study, they will contact the study team, and, if appropriate, make an appointment to be assessed as soon as mutually convenient. The diagnosis of an exacerbation will be made by the assessing clinician and appropriate treatment started. If the patient has been diagnosed as having an exacerbation of their disease by a different health care professional (eg, general practitioner, GP, or practice nurse), they will be advised to contact the study team as soon as possible to arrange an exacerbation assessment.

The Study Device: The N-Tidal C Capnometer

Description

The N-Tidal C data collector device is a novel infrared data collector capnometer that is intended for use by patients at home. It is a handheld device that measures the amount of CO_2 in the

user's breath during normal tidal breathing. It is simple to use; instructions for the patient are provided. The device set consists of the following:

- N-Tidal C Device x 1
- Mouthpieces x 6
- AA Batteries x 12
- Instructions for use (Participant's) x 1
- Quick start guide (Participants') x 1
- Storage case x 1

The mouthpieces should be changed each month.

The purpose of the device is to detect changes in the patient's exhaled CO_2 waveform. However, the purpose of this planned investigation is only to gather data on $TBCO_2$ waveforms using the N-Tidal C in different medical conditions and healthy volunteers; the device will not be used to inform actions or treatment for the patients.

CRiL is registered as a manufacturer of class 1 medical devices with the Medicines and Healthcare products Regulatory Agency. The N-Tidal C data-collector capnometer is the first of these, and a batch of 70 devices have been built to medical device Good Manufacturing Practices to meet the requirements of EN ISO 13485. All of the devices have been tested individually against set performance criteria as required for EN DIN 60601-90:1990, EN 21647:2004. All parts of the device that have contact with the skin, mouth, or lips have been constructed from medical grade plastic to mitigate biocompatibility risks.

Supply, Packaging, and Storage

The company has manufactured a batch of 70 N-Tidal C data collector capnometers, and each device will be allocated a unique serial number, allowing full tracking and traceability. The device history record will reference details of all major components and materials used in its manufacture. CRiL will supply sufficient N-Tidal C devices to the investigative site for each participant to have use of a single device. CRiL will also supply the replacement mouthpieces to the site for use by the study participants. Each participant will be supplied with six mouthpieces. The study site will be supplied with additional devices and mouthpieces for staff training and demonstration and as additional stock. The N-Tidal C devices and mouthpieces should be stored in a secure location at room temperature (10°C-30°C).

Administration

CRiL will provide appropriate training to study staff on the use of the N-Tidal C capnometer before the study commences. Additional support will be made available should it be required. In turn, the study staff will train the patients in the use of the device and will provide further training if needed. The N-Tidal C is for use in this study only and is not to be used for any other purpose. The investigator or designee will maintain a full record of device accountability. A device accountability log will be maintained detailing the dispensing and return of the study devices and mouthpieces. Used mouthpieces will be returned at the end of the study for inspection for contamination and degradation of performance; suitable containers will be provided to participants for the return of these items.

XSL·FO

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Device Use

The test will be performed as per the CRiL instructions. Participants will use the N Tidal C data collector device twice daily (morning and evening) and up to 6 times per day if the patient feels their condition is deteriorating or they are having an exacerbation. The capnometer recordings will be stored in the device until they are downloaded periodically throughout the study by the study staff. Participants will hold the device and breathe at their normal, relaxed rate of breathing into a disposable mouthpiece for 75 seconds. They will be asked to do this twice a day for the study period (until 6 months for all participants apart from those with pneumonia, who will cease follow-up at 2 months). The mouthpiece should be changed each month. It should not be used in crowded rooms, near a vehicle exhaust, open flames, cigarettes, immediately after drinking a hot beverage or a fizzy drink, or where there is a strong breeze. These conditions may interfere with the data capture of the device.

Disease Questionnaires

These will be completed only by the relevant cohort.

Asthma Control Questionnaire

The Asthma Control Questionnaire is a validated 7-item questionnaire for assessing the level of asthma control over the preceding 7 days. The questionnaire includes five symptom scores, the frequency of rescue bronchodilator use, and a measure of airway caliber (FEV_1% predicted). Responses are given on a 6-point scale, and the overall score is the mean of the responses (0=totally controlled, 6=severely uncontrolled). Scores over 1.0 are considered indicative of poor control [18].

Asthma Quality of Life Questionnaire

The Asthma Quality of Life Questionnaire is a validated 32-item questionnaire that measures the functional problems (physical, emotional, social, and occupational) that are most troublesome to adults with asthma. Patients are asked to think about how they have been over the previous 2 weeks and respond to each of the 32 questions on a 7-point scale (7=not impaired at all, 1=severely impaired). The overall score is the mean of all 32 responses [19,20].

Nijmegen Questionnaire (Breathing Pattern Disorder or Vocal Cord Dysfunction Cohort)

The Nijmegen score is derived from a 16-item questionnaire that collects information on symptoms related to hyperventilation, such as shortness of breath, feeling confused, palpitations, and tingling fingers. Answers are based on a 5-point Likert scale describing frequency of symptoms from "never" to "very often." A score of over 23 out of 64 suggests a possible diagnosis of hyperventilation syndrome, and the questionnaire can be used to assess the severity of the patient's symptoms during clinical assessments [21].

Dyspnoea-12 Questionnaire (Breathing Pattern Disorder or Vocal Cord Dysfunction Cohort)

The Dyspnoea-12 Questionnaire is a 12-item questionnaire that covers different aspects of breathing—eg, "my breath does not go in all the way," "my breathing makes me feel miserable,"

and "I feel short of breath." The patient is asked to tick the box that best reflects their breathing "these days" on a 4 point Likert scale (none, mild, moderate, and severe) [22].

Vocal Cord Dysfunction Questionnaire

The Vocal Cord Dysfunction Questionnaire is a 12-item questionnaire that has been validated in breathless patients with the condition and can differentiate vocal cord dysfunction from asthma. It rates the impact of 12 symptoms on a 5-point Likert scale (total score range: 12-60). It has also been shown to assess response to treatment [23].

Pittsburgh Vocal Cord Dysfunction Index Score

The Pittsburgh vocal cord dysfunction Index is a validated, easy to use clinical tool that assigns patients a weighted score based on symptoms of throat tightness (score of 4) and dysphonia (score of 2), the absence of wheezing (score of 2), and the presence of odors as a trigger for symptoms (score of 3). A cutoff of ≥4 has high sensitivity and specificity for the diagnosis of vocal cord dysfunction [24].

Kansas City Cardiomyopathy Questionnaire (Heart Failure Cohort)

The Kansas City Cardiomyopathy Questionnaire is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity, and recent change), social function, self-efficacy and knowledge, and quality of life (QoL). An overall summary score can be derived from the physical function, symptom (frequency and severity), social function, and QoL domains. For each domain, the validity, reproducibility, responsiveness, and interpretability have been independently established. Scores are transformed to a range of 0 to 100, in which higher scores reflect better health status [25].

Curb-65

The CURB-65 is a clinical prediction rule that has been validated for predicting mortality in community-acquired pneumonia. The score is an acronym for each of the risk factors measured. Each risk factor scores one point, for a maximum score of 5:

- Confusion of new onset (defined as an AMTS of 8 or less)
- Blood urea nitrogen greater than 7 mmol/l
- Respiratory rate of 30 breaths per minute or greater
- Blood pressure less than 90 mm Hg systolic or diastolic blood pressure 60 mmHg or less
- Age 65 years or older

A higher score indicates greater severity of disease and a higher risk of mortality [3].

Epworth Sleepiness Scale (Motor Neurone Disease Cohort)

The Epworth Sleepiness Scale (ESS) is a self-administered questionnaire with eight questions. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life [26].

Description of Respiratory Tests

Fractional Nitric Oxide

Fractional exhaled nitric oxide will be measured using a NIOX MINO device (Aerocrine AB, Solna, Sweden) or equivalent device for measuring exhaled nitric oxide level, as specified by the manufacturer's instructions and outlined in the American Thoracic Society and European Respiratory Society (ATS and ERS) standards [27]. This includes collection by controlled exhalation at the recommended controlled expiratory flow rate of 50 ml/s for greater than 6 seconds.

Spirometry

Spirometry will be conducted using a spirometer conforming to ATS and ERS standards as specified by the manufacturer's instructions [28]. Participants will inhale rapidly and completely from functional residual capacity, then will exhale in an initial blast of exhalation, and then continued exhalation until the end of the test. $FEV_1(L)$, FVC (L), $FEV_1/$ FVC ratio, FEF_{25-75}(% of predicted value), and peak expiratory flow (PEF; L/min) will be recorded. FEV_1, FVC, and PEF will be documented as both absolute values and as a percentage of the predicted value.

Full Body Plethysmography

Full body plethysmography will be performed conforming to ATS and ERS standards to assess static and dynamic lung volumes and airways resistance [29]. The functional residual capacity, residual volume, transfer factor (transfer factor for carbon monoxide), and transfer coefficient (carbon monoxide transfer coefficient) will be recorded as absolute values and as a percentage of the predicted value.

Arterial Blood Gas

Arterial blood gases (pH, FiO_2, pO_2, pCO_2, BE, HCO_3, SaO_2, and SPO_2) will be measured and recorded at every assessment visit for the MND cohort. If any additional assessments are taken as part of routine care while the patient is hospitalized or in the community, the details will be recorded on the case report form (CRF). For patients who are in hospital, arterial blood gas measurements will be performed using the hospital's standard equipment.

Chest X-Ray

A diagnosis of pneumonia will be made by either a respiratory physician or a radiologist on confirmation of consolidation on a chest X-ray for the pneumonia group. The location of the pneumonia will be recorded on the CRF.

Noninvasive Ventilator and Cough Assist Data

Only participants in the MND cohort who are established on home noninvasive ventilation will have their home ventilator data recorded on the CRF at their routine 3-monthly clinic appointment. This will include inspiratory positive airways pressure, expiratory positive airways pressure, average tidal volumes, hours of use of noninvasive ventilation, mask leak, and type of interface used (nasal or full face mask). These data will be taken off the ventilator and, if applicable, cough assist machine, and therefore will not include any additional testing for participants.

Description of Cardiac Function Tests

Transthoracic 2D Echocardiography

An echocardiogram is a test that uses ultrasound waves to measure the function and structure of the heart, including the heart valves and pressures within different chambers. It is part of routine care for patients admitted with an acute decompensation of their HF [30]. A comprehensive echo will be performed in accordance with the British Society of Echocardiography guidelines [31].

N-Terminal Pro-B-Type Natriuretic Peptide

The NT pro-BNP blood test will be performed on all patients in the HF cohort. This is a validated diagnostic and prognostic test for people presenting with HF and its assessment is part of the National Institute of Clinical Excellence guidelines [30].

New York Heart Association Class

The New York Heart Association classification is a routinely used functional assessment to classify the severity of HF purely based on assessment of impact of symptoms on daily activities. It places patients into one of four categories from class 1 (no limitation of physical activity) to class 4 (symptoms of HF at rest) [32]

Other Clinical Tests

Full Blood Count and Peripheral Blood Eosinophil Count

The full blood count will be taken and recorded in the asthma, HF, and pneumonia groups. In hospital, if further blood samples for routine hematological and biochemistry are taken, then these will be recorded in the CRF.

Skin Prick Testing

Asthma participants will have a skin prick test (SPT) performed to determine their atopic status. If the participant has had a SPT performed and recorded within the last 3 years, then this result will be used. A SPT is a simple and safe method of testing a person to determine whether or not they have an IgE-mediated allergic response to common inhaled allergens. SPT's will be performed by trained and experienced respiratory health care professionals, who are also trained in resuscitation techniques. Five common aero-allergens will be tested for: grass, house dust mite, aspergillus, and cat and dog dander. Atopic status will be demonstrated by a positive SPT (wheal diameter ≥3 mm larger than the negative control) [33].

Symptom Questionnaires (To Be Reported Three Times a Week via the Automated "Message Dynamics" System)

Asthma Cohort Symptoms

Asthma patients will report their symptoms 3 times a week (Monday, Wednesday, and Friday) via the automated telephone system provided by Message Dynamics. Each participant will be telephoned at a predetermined, agreed time of day. If the participant does not answer the initial telephone call, they will receive no more than two follow-up calls (maximum three in total). The presence or absence of four asthma symptoms during

a 24-hour period will be recorded (scoring 0 for absence of symptoms or 1 for presence of symptoms) alongside the number of times asthma reliever medication is used. This will provide a symptom score (from 0-4) and combined with the frequency of reliever medication used, a composite score (from 0-6, Table 1). Questions asked on the automated telephone system will be as follows:

1. Have you experienced regular wheeze in the last 24 hours? (yes or no)
2. Have you been woken at night by your asthma in the last 24 hours? (yes or no)
3. Has your asthma caused chest tightness in the last 24 hours? (yes or no)
4. Have you been more breathless than normal over the last 24 hours? (yes or no)
5. How many times have you used your salbutamol (ventolin) inhaler in the last 24 hours? (option 1: ≤2, option 2: 3-9, and option 3: ≥10).

A score ≥4 would alert the study team and prompt a member of the study team to call the participant.

Healthy Volunteer Cohort Respiratory Symptoms

The healthy cohort will be asked to record upper and lower respiratory tract symptoms 3 times a week via the automated telephone system provided by Message Dynamics. Each participant will be telephoned at a predetermined, agreed time of day. If the participant does not answer the initial telephone call, they will receive no more than two follow-up calls (maximum three in total). The presence or absence of three symptoms during a 24-hour period will be recorded (scoring 0 for absence of symptoms or 1 for presence of symptoms). This will provide a symptom score (range 0-3, Table 2). Questions asked on the automated telephone system will be as follows:

1. Have you had a runny or blocked nose in the last 24 hours? (yes or no)
2. Have you had any sinus pain in the last 24 hours? (yes or no)
3. Have you had a cough in the last 24 hours? (yes or no)

Breathing Pattern Disorders Cohort Symptoms

The BPD cohort will be asked to record presence of symptoms 3 times a week via the automated telephone system provided by Message Dynamics. Each participant will be telephoned at a predetermined, agreed time of day. If the participant does not answer the initial telephone call, they will receive no more than two follow-up calls (maximum three in total). The presence or absence of three symptoms during the previous 24-hour period will be recorded (scoring 0 for absence of symptoms, or 1 for presence of symptoms). This will provide a daily symptom score (range 0-3, Table 3). Questions asked on the automated telephone system will be as follows:

1. Have you had breathlessness in the last 24 hours? (yes or no)
2. Have you had chest tightness in the last 24 hours (yes or no)
3. Does your breathing feel tense in the last 24 hours? (yes or no)

Table 1. Symptoms present in the last 24 hours, reliever use, and assigned score.

Parameter	Score
Wheeze	1
Night waking	1
Chest tightness	1
Breathlessness	1
Maximum symptom score	4
Reliever use	
≤2	0
3-9	1
≥10	2
Maximum composite score total	6

Table 2. Upper respiratory and chest symptoms present in the last 24 hours and assigned score.

Parameter	Score
Runny or blocked nose	1
Sinus pain	1
Cough	1
Maximum score	3

Table 3. Symptoms present in the last 24 hours and assigned score.

Parameter	Score
Breathlessness	1
Chest tightness	1
Feeling tense	1
Maximum score	3

Table 4. Symptoms present in the last 24 hours and assigned score.

Parameter	Score
Breathlessness	1
Chest tightness	1
Fatigue	1
Leg swelling	1
Maximum score	4

Chronic Heart Failure Cohort Symptoms

The HF cohort will be asked to record symptoms 3 times a week via the automated telephone system provided by Message Dynamics. Each participant will be telephoned at a predetermined, agreed time of day. If the participant does not answer the initial telephone call, they will receive no more than two follow-up calls (maximum three in total). The presence or absence of four symptoms during the previous 24-hour period will be recorded (scoring 0 for absence of symptoms or 1 for presence of symptoms). This will provide a daily symptom score (range 0-4, Table 4). Questions asked on the automated telephone system will be as follows:

1. Have you had breathlessness in the last 24 hours? (yes or no)
2. Have you had chest tightness in the last 24 hours (yes or no)
3. Have you felt more tired than normal in the last 24 hours? (yes or no)
4. Have your legs swelled up more than normal in the last 24 hours? (yes or no)

A score ≥4 would alert the study team and prompt a member of the study team to call the participant.

Ease of Use Questionnaire for Participants

A brief self-completed visual analog scale questionnaire will be used to evaluate participants' opinions of the N-Tidal C device at the end of the study.

Test Acceptability Questionnaire for Staff

At the end of the study, a questionnaire will be used to evaluate health care professionals' opinions of the different study assessments. Informed consent will be obtained from each health care professional to participate within the study. Only health care professionals who taught and assessed the N-Tidal C device during the study to a minimum of 5 patients will be asked to participate.

Safety Assessment

Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant taking part in a clinical trial that does not necessarily have to have a causal relationship with the device under investigation. An AE can therefore be any unfavorable or unintended sign, symptom, or disease temporarily associated with the use of the device, whether or not this has a causal relationship with the device under investigation.

Adverse Device Event

Adverse device effects are all untoward and unintended medical occurrences in response to a medical device. All cases judged by either a medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualify as a device effect. This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.

Serious Adverse Events

A serious adverse event is any untoward medical occurrence that

- Results in death
- Is life-threatening. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Results in other important medical events

Other events that may not result in death, are not life-threatening, or do not require hospitalization may be

considered a serious AE when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious Adverse Device Effect

A serious adverse device effect (SADE) in a participant taking part in a clinical trial does not necessarily have to have a causal relationship with the device under investigation. However, a SADE is defined as any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device, which resulted in any of the characteristics or lead to the characteristics of a SADE.

A SADE is also any event that may have led to these consequences if suitable action had not been taken or an intervention had not been made or if circumstances had been less opportune. A SADE will be documented on a serious adverse event form.

Planned admission to hospital for a preexisting condition will not be considered an serious adverse event.

Recording and Reporting of Adverse Events

Participants will be asked about the occurrence of any AEs at each follow-up visit and will be asked to report AEs to their local study team between visits. AEs will be assessed by the principal investigator (PI) for causality, intensity, seriousness, and expectedness. Only AEs that have a reasonable possibility of being attributable to the device and any other AE considered to be of clinical significance by the PI as causing harm to the patient will be recorded in the CRF and reported to the sponsor as per their guidelines. Any AEs that do occur and are considered by the PI to be related to the device will be expedited to the sponsor, research ethics committee (REC), and the device manufacturer within 7 days. Lists of the AEs will be provided to the sponsor when requested.

Expected Adverse Events and Serious Adverse Events Exempt From Recording

In the different cohorts under investigation, participants may experience an expected deterioration in their condition and a number of serious or nonserious events throughout the course of the study. In the asthma group, participants may be expected to experience:

- An increase in rescue medication usage
- Additional courses of steroids for asthma exacerbations
- Increased unscheduled healthcare usage, including GP and emergency department (ED) visits for deteriorations in asthma control
- Time off work, college, or university because of worsening asthma control
- Hospitalization because of asthma exacerbation

In the HF group, participants may be expected to experience:

- Increase in their diuretic treatment
- Increased unscheduled healthcare usage, including GP and ED visits for deteriorations in their HF symptoms
- Further hospitalizations for acute decompensation of their heart failure.

In the MND group, participants may be expected to experience:

- An increase in medication use
- Additional courses of antibiotics for infections
- Increased unscheduled health care usage, including GP, ED. and high care visits for deteriorations in their MND
- Hospitalization because of worsening respiratory failure
- Natural progression of their MND leading to death.

In the BPD group, participants may be expected to experience:

- Increased unscheduled health care usage, including GP and ED visits for deteriorations in their symptoms
- An increase in any rescue medication use

Data Handling and Analysis

Data Collection and Management

Enrollment into the study will be documented in each participant's medical notes.

Data collection will comprise

- Paper CRF, including participant characteristics; disease severity; medication lists; clinical examination; and pulmonary, cardiac, radiological, and blood test results.
- Disease specific symptom, control, and QoL questionnaires.
- Paper self-completed questionnaire for participants.
- The N-Tidal C data collector recordings will be downloaded directly from the device onto computers supplied by the sponsor.

Data management will be conducted by CRiL. All data management procedures will be completed in accordance with CRiL Standard Operating Procedures. Before data being received in-house, it will be monitored at the investigator site. CRF and other data documentation removed from the investigator site will be tracked by the monitor. When errors in clinical data are discovered during data entry, a query will be created. Queries are created when information is missing or is illegible and needs further clarification. Query forms will be sent to the investigator for completion.

Data Analysis

Primary Analysis

All participants with recorded $TBCO_2$ waveforms will be analyzed. Subgroup analysis will be performed on the different study groups, namely, asthma, BPD, HF, MND, pneumonia, and healthy controls.

Analysis of End Points

Summary Statistics

Demographics or baseline characteristics of each of the study groups (asthma, BPD, HF, MND, pneumonia, and control) will be produced separately, as well as summaries for all groups combined. Normally, distributed continuous variables will be summarized by the mean and SD, whereas the median and interquartile range will be preferred for non-normally distributed continuous variables.

Primary Analysis

To establish our primary objective, CRiL will be using a variety of advanced analytic techniques to isolate the key characteristics in the capnogram that can identify each specific medical condition under investigation and to determine whether there is a difference between the different conditions. The team has developed algorithms to analyze specifics of the $TBCO_2$ waveform using modern computing technology. We will use an expert in machine learning to analyze the large dataset this study will produce. Specifically, we will analyze all components of the $TBCO_2$ waveform. The $TBCO_2$ waveform is made up of successive phases; phase 1 is a latency phase representing baseline inspired gas from the ventilatory dead space. Phase 2 is a rapid upward curving slope representing expired mixed air containing CO_2. Phase 3 is a plateau phase representing the partial pressure of CO_2 exchanged at the alveoli. The alpha angle (between phase 2 and phase 3 of the waveform), the peak end tidal CO_2 level, and the beta angle (between phase 3 and the inspiratory downstroke) will all be recorded. Novel parts of the waveform will also be analyzed as more information is found about the $TBCO_2$ waveform throughout the study. The analysis will include looking at the consistency of a participants repetitive breathing pattern, any changes between disease and healthy, and any changes between disease state (stable vs exacerbation).

Secondary Analyses

Associations between the recorded capnogram and other disease specific measures of severity, clinical condition (stable, exacerbating), and disease control will be examined.

Procedure for Dealing With Missing and Spurious Data

The analysis will include any measured data values, with missing values omitted from the analysis. No imputation of missing data will be performed. The data will be examined for outlying values. Where possible, these will be retained in the data analysis and their influence minimized by a data transformation or a nonparametric approach. If such approaches are not practical, the analysis of the primary outcome will be performed twice, with and without the outlying values.

Ethics

Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participant's identity document number on the CRF 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 that requires data to be anonymized as soon as it is practicable to do so.

Other Ethical Considerations

The study gained approval form South Central—Berkshire NHS Research Ethics Committee (REC reference 17/SC/0284) on July 17, 2017. The ethics committee reviewed and approved the protocol and all study relevant material such as the informed consent forms and PISs. 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 or favorable opinion from the REC and research and development 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. All participants will have adequate time to consider participation in the study, as per Good Clinical Practice guidelines [34].

There is a possibility that the study procedures reveal potential new, previously unknown disease pathology. This would be more likely to occur in our healthy controls. If such a circumstance occurs, then the participant will be told of the results and immediately referred to the most appropriate NHS department for further review. With the participant's consent, a letter will be written to their GP explaining the findings.

Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each person participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study using the PIS. The consent process will be documented in the participant's notes.

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice and any other regulatory requirements that might be introduced. The PI or delegate and the participant or other legally authorized representative shall both sign and date the informed consent form before the person can participate in the study. The participant will keep the PIS and a copy of the signed and dated consent form. The original will be retained in the trial master file. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes of when the PIS was provided and that informed consent was obtained for the study.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled.

Patient and Public Involvement

Patient and public involvement in this study has been obtained from patients with firsthand experience of living with breathing-related diseases. Initially, patients from our Wessex Asthma Network identified the need for new tools (especially for those with severe disease) to be developed and tested that allows them to reliably monitor their asthma at home or at the surgery or hospital, which does not involve forced breathing, and can alert them when an exacerbation is about to occur. If it could also detect whether someone has asthma or a different

cause of their breathlessness, then that would help many more people get an early diagnosis and treatment.

Working with patients in Wessex, we approached several innovators and UK companies to challenge them to produce new tools for people who suffer from conditions that affect their breathing. CRiL is such a company which has developed a unique tool (N-Tidal C) that could be used for exactly this purpose. Working with our patient advisors, we have designed a simple study with this new device that will compare information from patients with different breathing conditions to healthy people.

Our patient representatives have specifically contributed to the study design, screening and recruitment strategies, shape of the protocol, PIS, the lay summary, and the participant self-completion questionnaire. They are also satisfied that this study will not be excessively burdensome to participants.

Results

Recruitment to the General Breathing Record Study is ongoing. It is anticipated that results will be available by late 2018.

Discussion

The General Breathing Record Study will provide evaluation of a new handheld capnometer, the N-Tidal C. It will assess the use of capnography in differentiating different respiratory and cardiac diseases compared with healthy controls. It will provide some data on the use of capnography as a tool to detect deterioration in disease state. The study will also allow us to develop the device further in response to participant feedback.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Schedule of visit assessments.

[PDF File (Adobe PDF File), 44KB - resprot_v7i5e140_app1.pdf]

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Abbreviations

AE: adverse event
BPD: breathing pattern disorders
COPD: chronic obstructive pulmonary disease
CRF: case report form
CRiL: Cambridge Respiratory Innovations Limited
ED: emergency department
ESS: Epworth Sleepiness Scale
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
HF: heart failure
MND: motor neurone disease
NHS: National Health Service
NT-proBNP: N-terminal pro b-type natriuretic peptide
PEF: peak expiratory flow rate
PI: principal investigator
PIS: Participant Information Sheet
QoL: quality of life
REC: research ethics committee
SADE: serious adverse device effect
SPT: skin prick test
TBCO$_2$: tidal breathing carbon dioxide

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Viewpoint

Community Consultation for Planned Emergent Use Research: Experiences From an Academic Medical Center

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Abstract

Background: Emergent use research—research involving human subjects that have a life-threatening medical condition and who are unlikely to provide informed consent—in critical illness is fraught with challenges related to obtaining informed consent. Per federal regulations, to meet criteria to conduct such trials, the investigators have to seek community consultations. Effective ways of obtaining this consultation remains ill-defined.

Objective: We sought to describe methods, interpretations, and our experiences of conducting community consultation in a planned emergent use randomized controlled trial.

Methods: As part of a planned emergent use clinical trial in our study, community consultation consisted of four focus groups sessions with members from the community in which the clinical trial was conducted. Three focus group sessions were conducted with members who had an affiliation to Mayo Clinic, and the other focus group session was conducted with non-Mayo affiliation members. The feedback from the focus group sessions led to the creation of the public notification plan. The public was notified of the trial through community meetings as well as social media.

Results: As compared to community meetings, focus group sessions resulted in greater attendance with more interactive discussions. Moreover, focus group sessions resulted in greater in-depth conversations leading to institutional acceptance of the clinical trial under study.

Conclusions: Exception from informed consent can be acceptable to the community. Focus groups provided better participation and valuable interactive insight as compared to community meetings in our study. This could serve as a valuable guide for investigators pursuing exception from informed consent in their research studies.

KEYWORDS

qualitative research; research design; research ethics

Introduction

Background

Emergent use research may be defined as research involving human subjects who have a life-threatening condition and who are unable to provide informed consent. This type of research is important as interventions carried in an emergent setting may not undergo the same degree of scientific rigor that other interventions would in a nonemergent setting due to the requirement of informed consent. Informed consent forms the basis of patient autonomy. However, obtaining informed consent during emergent use research is often not feasible because of

the critical nature of potential participants' condition. Surrogates who could provide consent on behalf of the patient are frequently not immediately present and, even if they are, the situational context is usually such that approaching the patient's family about a research study is ethically questionable [1]. Regulations authorizing exception from informed consent for research conducted in emergency and critical care settings were approved by the Food and Drug Administration (FDA) in 1996 [2]. As part of this regulation, investigators must conduct an Institutional Review Board (IRB)–approved form of community consultation prior to the start of the study. They must also conduct community notification, the mechanism by which the local public is informed of the study. Community consultation can facilitate the building of trust while demonstrating respect within the community in which the study is to be conducted. During community consultation, the community is informed of the study prior to its launch with opportunities to give opinions about the study and engage in discussion with the investigators [3,4]. Dickert et al attempted to define the following four ethical goals of community consultation as (a) enhanced protection, (b) enhanced benefits, (c) legitimacy, and (d) shared responsibility [5]. Predefining these goals specific to each study can help organize time, objectives, and resources, both for researchers as well as IRBs.

Community consultation can be conducted in numerous ways. It has been differentiated by some into interactive and noninteractive methods [4]. Focus groups, community/town hall meetings, in-person interviews, investigator-initiated or existing group meetings comprise the interactive methods, whereas personal or Web-based surveys are examples of noninteractive methods. In a recent multicentered study by Dickert et al, interactive community consultation methods demonstrated significantly increased acceptance to participate, recall, and understand the study as compared to noninteractive methods [4]. Several other single-center studies have shown similar results [6-8]. Although interactive methods also showed significantly higher variability and lower recall of risks associated with the study, they offered a unique opportunity to explore the views and concerns of the participants. Our study entitled "Ketamine/Propofol Admixture 'Ketofol' at Induction in the Critically Ill Against Etomidate: KEEP PACE Clinical Trial" met FDA definitions to qualify as planned emergent use research [9]. Thereafter, as per FDA requirement, a plan for community consultation and notification was developed. Our aim was to conduct two interactive forms of community consultation (focus groups and community meetings), describe our experiences with both methods, and to demonstrate how our consultation plans led to public notification.

Methods

Community Consultation

We used focus groups for our community consultation, inviting participants from local communities most likely to be under investigation. We conducted focus group sessions using standard approaches [10]. Focus group participants were notified via flyers and research announcements surrounding Mayo Clinic Rochester and Olmsted Medical Center (OMC). Adults (≥ 18 years) were asked to join a focus group to share their views on consent for an upcoming clinical trial. Refreshments were served with sandwiches prepared at each session. Questions asked by the moderator centered on reasons for conducting the study, how a patient may be a potential participant, and if so, how they would feel about enrolling into a research trial without knowingly giving permission. All focus groups were led by a trained moderator (JM). We used focus groups because we believed the opportunities to explore community members' views and concerns would be indispensable for our study, considering the critical nature of the intervention. The information received and interpreted from these discussions was then integrated and disseminated through community notification. Formal analyses performed from the focus group sessions were not performed as this was a descriptive study by nature. Additionally, as recommended by our IRB, de novo community meetings were organized in a similar manner as the focus groups and conducted to provide information and answer further questions as part of the community notification plan. Community-engaged research is typically conducted in the form of public (community) meetings at our institution. Hence, the recommendation from the local IRB. We expected to observe that of the two forms of interactive methods, focus group sessions would provide more valuable insight into community views given the smaller setting in which these were conducted.

Community Notification

Notification included a summary of all key aspects of the study, including the nature of planned emergency research, study protocol, medications, patient participation, waiver of informed consent, and links to information about the study and the investigators. Our community notification plan was developed in accordance with the FDA regulations as well as inputs from focus group discussions (community consultations) regarding utilizing traditional and social media.

Results

Community Consultation

Three focus group sessions were conducted on the Rochester Mayo Clinic campus and one was conducted at OMC facility. OMC is the other primary healthcare provider in Rochester besides Mayo Clinic. It has a smaller research arm, and OMC patients usually do not have a direct Mayo affiliation (employment, spousal employment, and retiree) and thus are likely not to participate in the study. In total, we had 27 participants in these sessions; 11, 6, 5 and 5 in each session respectively. It was clear to the investigators that participants involved in the focus group session at OMC were more skeptical of research than the three focus group sessions done at Mayo Clinic. Participants from all focus groups were supportive of the study and understood that obtaining informed consent was not practical or "feasible" for the study. Focus group members concurred that study participants and/or surrogates "need to be informed of study participation." There was a general consensus that the "exact timing" and approach for notifying the subjects would need to be "contextual and determined on a case-by-case basis."

In our trial, after the acute event has passed and when time is considered appropriate, our study coordinator informs the patient or the surrogate verbally as well as in written content about the patients' enrollment. In the event the patient is deceased, the surrogate is approached through the same process, but within a 48-hour window from the time of death. A consistent theme among focus group members was also the need for research subjects or surrogates to be "able to withdraw their participation by having their data not used in the study." Interestingly, this theme was not brought forward by the moderating team, but rather it was spontaneously raised by the participants. With further exploration, focus group participants expressed that "data removal," even after the fact, "was congruent and one in the same as the participant undergoing informed consent." Because this was a substantial theme and is consistent with local values of the community, we have incorporated this into our study design. An opt-out mechanism through development of "community wide opt out registry" was thought to be "neither necessary nor helpful" by our focus groups.

Unfortunately, we did not have meaningful attendance at our community meetings. Thus, our notification plan relied on the feedback from the focus group sessions.

Community Notification

Our focus group participants generally agreed that the plan of publishing information about the study in the local newspaper was valuable; however, several other papers and newsletters with local circulation were suggested. Participants also agreed that making radio announcements were a good idea, but suggested considering regularly scheduled radio shows as well as utilizing ethnic radio and television stations available in our community to reach immigrant populations, who may not be fluent in English. Notices of our study are being published in the area's largest daily newspaper approximately every 2 weeks and in local circulars with a different target audience. In the current trial, our first public notification meeting had no attendees. To broaden the public access to our study information, a YouTube video about 9 minutes in length was created [11]. To date, the video has been viewed 481 times. Another strategy utilized during our trial was to provide the same video through our hospitals "on-demand" video system and post information in our intensive care units and their corresponding waiting rooms, allowing patients and family members to access the video and receive information about the trial.

Discussion

Focus Groups

Feedback obtained from our focus group sessions played a pivotal role in formulating the plan for prospective waiver of consent, later retrospective collection of consent, and the public notification plan. In particular, the feedback on data withdrawal after enrollment into the trial was extremely valuable as data withdrawal after the fact is not supported by federal regulations and thus was paramount in formulating our consent plan. Furthermore, the timing of enrollment notification was invaluable and served to establish the time period on when to approach patients or their surrogates about trial enrollment. This is an important milestone to strive for when community

consultations are performed and failure to acknowledge community concern is not desirable. We conducted four focus group sessions. Prior literature indicates that conducting overly extensive consultation may obstruct important work versus insufficient consultation that can be ineffective [5]. Given the recurring themes with each session and no new themes during our last session, we felt that further consultation would likely be ineffective.

Community Meetings

Interestingly, we were not able to generate meaningful attendance from participants in our investigator-initiated community meetings. Although the community meetings were part of the community notification plan in our study, they can be included within community consultation, as both involve participation from the community, whether seeking advice or consent. To our knowledge, a comparison of efficacy between such community meetings and focus groups is not currently found in the literature. The difference in response is probably multifactorial, depending more on regional factors or incentives offered. In addition, this observation may be explained by the fact that these were de novo meetings and not current existing meetings for the public. Targeting existing community group meetings showed a good attendance in a recent multicenter study [4].

Institutional Review Board

Throughout the process of conducting and planning this particular trial, we faced several challenges from the local IRB. Currently, our institution has never served as primary sponsor of a planned emergent-use research study. The reservations our IRB had regarding planned emergent use research centered on patient autonomy. The IRB felt that without patient autonomy, the trial was unethical and therefore requested an alternative to prospective informed consent; thus leading to the creation of data withdrawal for those subjects who later declined participation in the trial. Retrospective consent is obtained when the data is already established. This form of consent allows, to a degree, patient autonomy. However, this is in direct conflict with the FDA and their requirements for studies conducted under planned emergent use research. The removal of data could potentially bias the study results as those most likely to die may request that their data be removed due to interventions labeled as research, more so than those who had a favorable outcome. Following several meetings with both regulatory boards, we allowed data removal on study procedures that were to be performed after talking to the patient and/or legally authorized representative. However, data obtained up to that point is considered part of the research without removal. This re-enforced the context-sensitive nature of informing the participants of their enrollment into the study.

Limitations

In our study, we attempted to capture a diverse range of opinions through attempts to incorporate views of subjects that are not the target population and most likely to have reservations against participation in research (OMC participants). These inclusions by all means could not have been complete. A quantitative analysis defining level of trust, understanding, and acceptance

of participation was not performed. This can be an important prospect for future studies as there are currently limited empirical data on the effectiveness of consultation strategies.

Conclusions

Choosing an appropriate community consultation method for exception from informed consent continues to pose a challenge for the research community and the IRB. Lack of definite benchmarks and knowledge about the kind of methods best suited for each kind of study warrant research in this area. In these circumstances, it may be beneficial to recommend the presence of IRB members at such sessions. This would help illustrate efficacy of each method to ensure autonomy and respect of study subjects and would also improve the dynamics of understanding between research teams and IRB. For example, having an IRB member present during discussions regarding data use/removal would have streamlined the process and would

have demonstrated to the institutional body the community views on patient autonomy. We have attempted to describe our experience with obtaining and interpreting community consultations as well as conducting community notifications. We intend for these experiences to serve as a guide for novel emergent use researchers and a stepping stone for further multi-centered research studies.

Future Directions

It would be of benefit to perform comparative studies between the different community participation events available and to delineate the efficacy of each method in relation to the kind of study being conducted. As our study posed a higher risk of death with some important decisions that were dependent on interpretations of community consults (eg, data gathering), we feel distinct interactions in focus group sessions are beneficial for studies similar to ours.

Authors' Contributions

JBM and RFH carried out the focus group sessions and drafted the manuscript. NJS and RFH coordinated IRB meetings. JP executed and coordinated the community notification plans as well as drafting the manuscript. NJS conceived of the study and participated in its design and coordination and helped draft the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

FDA: Food and Drug Administration
IRB: institutional review board
OMC: Olmsted Medical Center

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