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PROTOCOL FOR A PILOT RANDOMIZED CONTROLLED TRIAL OF AN EDUCATIONAL PROGRAM FOR ADULTS ON CHRONIC HEMODIALYSIS WITH FATIGUE (FATIGUE-HD)

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ABSTRACT

Introduction

Fatigue is a pervasive symptom of end-stage renal disease (ESRD) that has been identified as a top research priority by patients. We developed a personalized, web-supported educational program (the PEP Program) to teach people with ESRD to use energy management to manage fatigue. Preliminary studies have demonstrated positive effects on fatigue and disability, justifying the need for a randomized controlled trial to better understand the efficacy of the program. The objectives of the pilot RCT are to estimate RCT eligibility, recruitment and attrition rates; inform the primary outcome measure and sample size for the RCT; and evaluate treatment fidelity among program administrators.

Methods and Analysis

A parallel-arm, 1:1 pilot RCT will be conducted at four in-centre hemodialysis units in Calgary, Alberta, Canada. People on hemodialysis who report moderate or severe fatigue based on routine reporting of fatigue scores, and meet other study eligibility criteria, will be invited to participate. Consenting participants will be randomized to undergo the 7-9 week "PEP" program or an active control, and followed for 12 weeks after the program concludes. Information on eligibility, recruitment and attrition rates will be collected, and questionnaires assessing fatigue and life participation will be administered pre-intervention, mid-intervention, immediately post-intervention, and 12 weeks post-intervention. Analyses will include calculation of eligibility, recruitment and attrition rates; power considerations for the full-scale RCT; and evaluation of treatment fidelity of program administrators.

Ethics and Dissemination

Risks associated with this study are minor. Patients may experience discomfort while filling out study questionnaires. They will be advised to skip any questions that make them uncomfortable. Potential benefits of participating include any benefit derived from the study intervention, and contributing to research that may benefit people with kidney disease in the future. Trial results will be disseminated via publication in an academic journal and presentation at academic conferences.

ARTICLE SUMMARY

Strengths and Limitations of this Study

- The pilot RCT protocol was developed in accordance with SPIRIT guidelines
- Use of an extensive standardized training protocol for the study intervention to maximize treatment fidelity across program administrators
- Use of an active control condition and blinding of patients and outcome assessors to treatment allocation status, to control for placebo effect
- Exclusion of non-English speaking patients limit its generalizability to non-English ESRD populations
- Non-blinding of treatment administrators may introduce undue bias into study

CLINICAL TRIAL REGISTRY NUMBER

The trial is registered at www.clinicaltrials.gov. Trial identifier: NCT03825770

STUDY INVESTIGATORS

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SPONSORS/SOURCES OF FUNDING

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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None.

KEYWORDS

Fatigue; Renal dialysis; Renal Insufficiency, Chronic; Rehabilitation; Randomized Controlled Trial

DATA STATEMENT

Not applicable (study protocol)

INTRODUCTION

Fatigue is a highly common and problematic symptom experienced by people with end-stage renal disease (ESRD)(1). Fatigue has been defined as an "unusual, excessive or whole body tiredness, disproportionate or unrelated to activity or exertion" (2), and is purported to occur in people with ESRD due to physiological (eg. anemia, inflammation), psychological/behavior (eg. depression, sleep disorders), and/or treatment-related factors (eg. postdialysis fatigue). Fatigue is associated with low quality of life(3,4) and disability(5,6) in the ESRD population, and its impact on life participation (ie. the ability to participate in meaningful day-to-day activities) has been identified as a top research priority by ESRD patients(7). There are currently few well-studied and viable treatment options to address fatigue in the ESRD population(8); existing approaches are either already in use (eg. Erythropoietin therapy) or challenging to deliver and maintain (eg. exercise). As a result, there are currently a dearth of treatments available to help ESRD patients manage fatigue and mitigate its effects on their life participation.

Energy management education (EME) is an approach that has been associated with reductions in fatigue and/or improvements in life participation in other chronic disease populations, such as multiple sclerosis(9–11) and cardiac disease(12,13). The theory underlying EME is that fatigue in people with chronic diseases is exacerbated by a mismatch between energy capacity and day-to-day energy expenditure. The goal of EME is therefore to provide people with practical strategies (eg. prioritizing, using efficient body postures, organizing the home environment) to reduce their energy expenditure during everyday life. EME may be a good fit for people with ESRD, as they often have a reduced energy capacity compared to healthy populations (6), and expend extra energy on routine dialysis management tasks (eg. planning and preparing renal-

friendly meals; attending dialysis or performing home exchanges). However, EME has never been tested in the ESRD population.

We developed a personalized, web-supported EME program (the "PEP" Program), tailored for the ESRD population. The program is designed specifically to reduce the impact of fatigue on life participation, and is delivered in a flexible, web-supported format to accommodate patients' demanding dialysis schedules. Preliminary usability and acceptability testing found that the program was well received, while several single-case studies found that people with ESRD experienced a small to moderate decrease in fatigue and disability after participating in the program. These positive preliminary findings justify a randomized controlled trial (RCT) to more conclusively establish the efficacy of the PEP program.

However, additional information is first needed to design and plan an RCT. First, we need to establish the feasibility of an RCT on the PEP program. Poor recruitment and high attrition rates are common in clinical trials involving ESRD patients, with high illness burden as one possible factor. This could be problematic for a study of an educational program like the PEP program, that will require substantial patient engagement and participation. Second, we need to understand the feasibility of training non-rehabilitation clinicians (eg. nurses) to administer the PEP program for future knowledge translation and program planning purposes, as rehabilitation therapists (who typically administer energy management education programs) are often absent from dialysis units. Finally, we need to collect more data on the effects of the program on possible primary outcomes (fatigue and life participation) to determine the optimal primary outcome measure for an RCT, estimate the sample size for a an RCT, and establish maintenance of short-term effects of the PEP program on patient fatigue and life participation.

OBJECTIVES

Primary Objective

1. To estimate the proportion of ESRD patients that are eligible for an RCT of the PEP program, will consent to participate, and will complete all study procedures

Secondary Objectives

1. To identify the fatigue or life participation outcome measure that is most sensitive to change related to the intervention, and estimate the treatment effect size and variability for RCT sample size calculations

2. To explore the maintenance of gains in fatigue and life participation after the PEP program at 3 months post-treatment

3. To examine treatment fidelity to the PEP program among non-rehabilitation clinical staff

METHODS

Trial design

Parallel group, 1:1, pilot randomized controlled trial.

Participant Identification

Participants will be recruited from four in-center hemodialysis units in Calgary, Alberta, Canada. Patients who would be potentially eligible and interested in the study will be identified by clinical staff and approached to assess their interest in the study. Interested patients will undergo a comprehensive informed consent process. Written informed consent will be obtained before any study procedures are undertaken. Consenting participants will undergo full eligibility

screening using the study eligibility criteria (Table 1). Consenting and eligible patients will be invited to participate in the study.

Table 1: Study Eligibility Criteria

Inclusion criteria	Exclusion criteria
1. Aged ≥18 years 2. On chronic dialysis therapy for ≥3 months at time of recruitment 3. Clinically and cognitively stable (able to provide informed consent) 4. Scores an avg. of ≥4 on items 5, 7 , 8 and 9 of the Fatigue Severity Scale	1. Inadequate written and verbal English comprehension for study activities 2. Plan in place to discontinue in-center hemodialysis at participating center within 6 months of time of recruitment (due to modality change, relocation, transplantation, or dialysis withdrawal) 3. Resides in a nursing home facility 4. Preclusive visual impairment

Randomization and Concealment

Participants will be allocated equally (1:1) to intervention or control. Permuted blocked randomization with randomly varied block sizes of 2-4 will be performed, and randomization will be stratified by dialysis unit. Participants will be allocated using a computer-generated random number sequence. Randomization will be performed by a research team member who is not involved in other aspects of the study, to maintain allocation concealment.

Blinding

Study participants will be blinded as to which treatment condition is the true treatment under study (intervention or active control). All patient study materials and communications will be left vague, describing the study purpose as being an investigation of an "educational program" for

adults with fatigue. Blinding of treatment administrators will not be feasible, given their required level of familiarity with both the treatment and control conditions.

Treatment: The "PEP" Program

Participants randomized to the treatment condition will undergo the "PEP" (Personal Energy Planning) program. The PEP program is an energy management education program that combines general education about energy management with individualized training to develop personal energy management strategies. The program is delivered over 7-9 weekly sessions, that are ~20-30 minutes in duration and administered either in person or via telephone (based on patient preference). The program will be administered by a trained study clinician (occupational therapist or nurse). It consists of two parts that are described below.

Part 1: Participants complete two educational computer modules (20-30 mins each) that explain basic principles related to energy management (eg. energy budgeting; prioritizing; seven key energy-saving strategies), and include activities and exercises to reinforce key concepts. The modules are publicly accessible online (www.pepmodule1.com; www.pepmodule2.com), and can be completed by patients independently (with support provided to access technology, as needed).

Part 2: Participants learn how to apply the energy management principles from Part 1 to accomplish their own life participation goals. First, participants work with a study clinician to identify 3 personal life participation goals (eg. to be able to do the grocery shopping weekly). They then complete a web module (www.pepmodule3.com) that explains a method to identify *personalized* energy management strategies that will facilitate their goals. The method used is an adapted version of the Cognitive Orientation to Occupational Performance (CO-OP) intervention(14), which is an evidence-based approach to cognitive skill acquisition(15). Key

elements of CO-OP used are dynamic performance analysis (ie. analyzing where the participant is expending excessive amounts of energy during each goal activity); goal-plan-do-check (ie., generating energy management "plans", "doing" the plans, and "checking" to see if they work), and guided discovery (a method of questioning and cueing used by the study clinician to enable the participant to discover energy management solutions themselves). Participants spend 5-7 program sessions (15-30 mins each) applying the CO-OP approach with the study clinician to develop and test personalized energy management strategies for accomplishing their goals. The process is continued until an optimal performance solution is found for each goal; or, the program maximum of 9 weekly treatment sessions are reached (whichever comes first). Participants are also given a program workbook to guide them throughout the PEP program.

Control: General Information about Kidney Disease

Participants randomized to the control condition will review information from the Kidney School learning modules (16), during 6-8 individual sessions with a trained study clinician (occupational therapist or nurse). The modules contain general information about managing kidney disease, addressing topics such as diet and heart health. Sessions will take place either in person or via telephone (based on patient preference). Use of this active control condition will minimize the risk of bias associated with patients receiving extra staff attention during the treatment condition.

Treatment Adherence

Study coordinators will monitor and encourage participant adherence to the treatment protocol during weekly visits. All missed or incomplete treatment sessions will be documented.

Staff Training

All treatment administrators will undergo training in how to administer the treatment and control

protocols. A training manual for treatment and control conditions will also be provided. Training materials can be obtained by contacting the study corresponding author.

Concomitant Care

Patients enrolled in the trial will continue to receive and undergo all usual clinical care activities. Changes in clinical care or status during the study that could influence outcomes of fatigue and life participation (eg. exercise regimens; hemoglobin level changes) will be documented.

Data Collection

Demographic and clinical data (Table 2) will be collected for each consenting participant at the time of their first study visit by a trained study assessor, either through chart review or participant interview.

Table 2: Demographic and clinical study variables

Demographic	Clinical
Age	Dialysis vintage
Sex	Comorbidities
Residence type	Most recent hemoglobin
Living status	Most recent albumin
Marital status	ADL independence
Employment	Cognitive function (MiniCOG)
Education	Depression (PHQ-2)

The number of screened patients who meet study inclusion and exclusion criteria; consent to participation and randomization; and complete all study procedures will be documented by study

staff. Follow-up information (including recent hospitalizations, illnesses, dialysis changes, exercise changes, lab data) will be documented at each follow-up visit.

The following questionnaires of fatigue and life participation will be administered at four timepoints (Figure 1), except the COPM, which will not be administered at Baseline. The 4 timepoints are: Baseline (at first study visit); Post-Part 1 of the PEP program (just prior to commencing Part 2, session 1); Post-Part 2 of the PEP program (one week after the final study visit); and 12 weeks after the final study visit. Questionnaires will be completed before, during, or after a dialysis session, according to participant preference. The timing and location of questionnaire completion will be kept consistent across assessment timepoints for each participant.

Fatigue Severity Scale (FSS)

The FSS(17) asks individuals to rate, on a Likert scale from one to seven, the severity of their fatigue and its impact on their life during the past week. The FSS is a valid, reliable and responsive measure(18,19) that has previously been used in the dialysis population(20).

Fatigue Management Questionnaire (FMQ)

The FMQ asks participants to rate various aspects of their fatigue management (eg. competence, satisfaction, self-efficacy) on a Likert Scale of 1-10. The questionnaire was created for this study to fill a gap in assessments that measure competence and self-efficacy specifically related to fatigue management.

Modified Fatigue Impact Scale (MFIS)

The MFIS(21) is a 21-item Likert-based scale that assesses the effects of fatigue on physical,

cognitive, and psychosocial functioning. The Fatigue Impact Scale has frequently been used as an outcome measure in energy management education studies.

Reintegration to Normal Living Index (RNLI)

The RNLI(22) assesses the degree to which individuals who have experienced traumatic or incapacitating illness achieve reintegration into normal social activities, using 11 declarative statements that are accompanied by a visual analogue scale (VAS). The RNLI has been found to have strong validity and reliability in multiple disease populations(23).

Canadian Occupational Performance Measure (COPM)

The COPM(24) is designed to capture a client's self-perception of performance in three specific priority tasks of everyday living. It asks individuals to rate, on a 10-point Likert scale, the importance of three self-chosen priority activities; their current perceived performance on the priority activities; and their satisfaction with that performance. The COPM has been found to be a valid, reliable, clinically useful and responsive outcome measure in multiple disease populations(25).

All treatment sessions (excluding computer modules) will be audio-recorded on an audio recording device, to allow for evaluation of treatment fidelity of the program administrators using the CO-OP fidelity checklist. The checklist includes 26 items, each scored on a scale of 0-5, that measure the extent of use of various key elements of the treatment approach by the treatment administrator.

Data Management & Confidentiality

Study data will be recorded onto standardized paper study forms at the time of collection. Data will be anonymized by assigning each participant an unidentifiable study ID number at the time

of enrolment that will be used to identify them for all study materials. Paper data forms will immediately be filed and stored in a locked office area, and signed study consent forms will be filed and stored separately from data forms to maintain participant anonymity.

Study data will subsequently be entered into a secure database by a research assistant. The database will be password protected and stored on a secure server, with access restricted to authorized users of the server. Range checks for data values will be performed after data entry, to promote data quality.

Audio recordings of study sessions will also be transferred onto a secure server, and deleted from their original recording device at the time of transfer. A sample of the audio recordings will subsequently be transcribed into text by the team transcriptionist and stored on the secure server. Data files and documents will be destroyed 7 years after the project is closed.

Protocol Deviations and Amendments

Protocol deviations are reported in Table 3. Any mid-study protocol modifications will be submitted to co-investigators and REB for approval and communicated to study participants and the trial registry once approved.

Table 3: Protocol Deviations

Protocol Deviations
a. Failure to initiate treatment within 2 weeks of study screening & enrolment b. Missed ≥3 consecutive treatment or control sessions, leading to discontinuation of assigned treatment condition (but not withdrawal from study)

c. Missed ≥2 consecutive study assessment visits, leading to non-completion of an assessment package (but not withdrawal from study)
d. Participants switch ESRD treatment modality during the course of the study
e. Participants are hospitalized overnight during the course of the study
f. Dropouts and their causes (eg. withdrawal of consent* or transfer to another centre)

Missed Study Treatment or Assessment Appointment

Missed study sessions will be addressed as outlined in Table 4. The study treatment and assessment schedule has been designed with flexibility to accommodate the frequent changes in health status and fatigue levels experienced by this population, which may cause occasional missed study appointments.

Table 4: Protocol for Missed Study Sessions

Missed Session Details	Response
Participant misses 1-2 consecutive weekly treatment sessions	-Missed appointment(s) will be documented -The scheduled treatment session will be delayed until the next weekly session -Dates of remaining assessment and treatment sessions will be delayed accordingly
Participant misses 3 or more consecutive weekly treatment sessions	-Missed appointments will be documented -Treatment protocol will be discontinued -Treatment discontinuation will be recorded as a Protocol Deviation

	-Assessment schedule will carry on as planned, regardless of missed treatment sessions
Participant misses scheduled assessment appointment date and does not complete it during the week of the scheduled date, but completes it the following week	-Missed appointment date will be documented -The scheduled assessment will be delayed to the following week -Dates of remaining treatment and assessment sessions will be delayed accordingly
Participant misses scheduled assessment appointment by **>1 week**	-Missed appointment will be documented -Missed assessment will be recorded as a Protocol Deviation -No additional attempts will be made to complete the missed assessment

Data Analysis

Demographic and clinical data will be reported as means and standard deviations for continuous parametric data; medians and ranges for continuous nonparametric data; and frequencies and percentages for categorical data.

The proportion of patients meeting each of the feasibility endpoints (eligibility, recruitment and attrition rates), with accompanying 95% confidence intervals, will be calculated.

Assuming a normal distribution, standardized effect sizes for each fatigue & disability outcome measure will be calculated for both immediate post-intervention and three months post-intervention, as follows:

$$\text{Cohen's D} = \frac{\text{Mean pre-post change (treatment)} - \text{Mean pre-post change (control)}}{}$$

Standard deviation (pooled)

These data will be analyzed using intention-to treat analysis. Sample size calculations for the RCT will be made using the treatment effect size and variance estimates from the immediate post-intervention change data for the selected outcome measure. Missing follow-up data will be addressed using pairwise deletion.

The treatment fidelity of treatment administrators will be analyzed by calculating an average score out of 5 on the CO-OP fidelity checklist, for one treatment session per participant randomized to the treatment condition.

SAMPLE SIZE AND FEASIBILITY

A sample size of 40 patients (20 per treatment arm) was chosen to provide a sufficiently precise estimate of the treatment effect for RCT sample size calculations(26), given 80% power, a small-medium effect size on fatigue/life participation, and an anticipated attrition rate of ≤20%. There are approximately 425 prevalent patients on hemodialysis in total at the four participating clinical sites. Estimates of eligibility and recruitment rates based on existing literature suggest that this patient pool will be sufficient to achieve the target sample size.

PATIENT AND PUBLIC INVOLVEMENT

Patients have been involved, both directly and indirectly, in multiple aspects of this research project. The intervention under study was developed in response to results of patient engagement research, which identified a need to further investigate fatigue management in renal disease(7). Patients were involved in the development of the intervention under study, providing

consultation and feedback on the first intervention prototype that led to several program modifications. Patients were also consulted on the content and format of the control condition to be used in this study. Our current study team includes a patient partner who will be consulted about patient-related issues that arise during the study, the interpretation of results, and strategies to optimize dissemination and uptake.

ETHICAL CONSIDERATIONS

Risks and Benefits

As part of their baseline assessment, participants will complete the PHQ-2 depression screening assessment. This assessment may identify individuals who have, or are at risk for, clinical depression. Any individual who scores >2 on the PHQ-2 will be offered connection to support services, such as referral to their clinical social worker, or to a local counselling centre. Study participants will also have to complete several study questionnaires, and participate in PEP program treatment sessions. There is a risk that patients may experience short-term fatigue, or, uncomfortable or unpleasant emotions in response to some of the questions in the study questionnaires. Participants will therefore be advised that they can skip any questions or study procedures that make them uncomfortable.

Direct benefits of participating are those which may be gained from completing the study intervention, such as improved fatigue management, improved knowledge about kidney disease, and/or and increased staff attention. Indirect benefits include the potential that others with kidney disease may benefit from the study findings in the future.

Data Safety and Monitoring Board (DSMB)

As the proposed study is small and its risks to participants are low, a DSMB is not needed. Monitoring for potential risks (eg. fatigue, discomfort) will be performed by those interacting directly with the patient during the study (the study clinicians and assessor). If any unexpected concerns arise that cannot be immediately mitigated, the concerns will be brought forth to the PIs for further discussion and decision-making.

Research Ethics Approval

Ethics approval for the study has been obtained from the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary.

DISSEMINATION PLAN

Trial results will be disseminated to patients with a summary sheet that will outline the trial findings in lay language. Results will be disseminated to healthcare professionals and researchers via publication in an academic journal and presentation at academic conferences.

DISCUSSION

Fatigue is a common and disabling symptom of end-stage renal disease(1,4–6), that is currently challenging to address due to its complex, multifactorial etiology. Recent results from patient-reported outcome and engagement studies have highlighted the need to explore new fatigue management interventions for people with ESRD(5,7). For example, population-based data from Ontario, Canada revealed that half of patients on in-center hemodialysis experience moderate to severe fatigue, while fatigue has been identified as a top research priority by patients with ESRD in a national Canadian research priority-setting exercise(7). Energy management education

(EME) is a fatigue management approach that has been associated with positive results in several other chronic disease populations. In people with MS, studies including RCTs have found EME reduces patient fatigue and its impact on physical, cognitive and psychosocial functioning, and improves self-efficacy (8–10,23,24). Earlier-phase studies in acquired brain injury(29), cardiac disease(12,13), and post-polio(30) have similarly shown positive effects on fatigue and related outcomes. However, EME has yet to be empirically investigated in the ESRD population. Preliminary findings on EME in ESRD patients have been positive regarding its effects on fatigue and independence, suggesting the approach has potential to fill an important gap in ESRD care. However, studies have thus far lacked important design elements, such as blinding and randomization. The proposed pilot RCT will provide necessary feasibility information to conduct an RCT that can more conclusively establish the efficacy of the PEP program in the ESRD population.

The proposed pilot RCT has a number of strengths. The program under investigation (the PEP program) has been tailored specifically to meet the needs of the ESRD population: it is designed to facilitate participation in meaningful activities, which is a high priority for ESRD patients, and is delivered in a flexible format to accommodate the dialysis schedule. Patients have also been consulted and provided input at several stages of intervention development and testing. The study protocol was developed using the SPIRIT guidelines for a pilot RCT protocol, increasing the likelihood that important study design elements have been addressed. We have also developed a standardized training and administration protocol for the PEP program, that we anticipate will maximize treatment fidelity and consistency across program administrators. An

active control condition to blind patients to their treatment allocation status will further increase the confidence in our study findings, by controlling for the placebo effect.

Our study also has limitations. First, we are excluding non-English speaking patients from the study, which limits its generalizability to non-English-speaking ESRD populations. However, the findings from this study may help to justify developing program materials in alternative languages that are accessible to a wider range of renal patients. We are also excluding patients outside of the in-center hemodialysis population who also experience a high burden of fatigue (eg. predialysis patients, peritoneal dialysis patients, home hemodialysis patients). This study should be viewed as an important first step in establishing the potential for the PEP program, that can lay the groundwork for future research into energy management education in other renal populations. Finally, we are unable to blind treatment administrators to treatment allocation, due to our inability to conceal which study condition is the treatment condition. We perceive blinding to be unfeasible because treatment administrators would be able to identify the treatment condition, based on inequities between the two conditions in the amount of content dedicated to fatigue and the length of time spent on staff training. The infeasibility of blinding is a well-recognized limitation of trials studying psychosocial or behavioural interventions that are not easily matched with an equivalent control.

In conclusion, the findings from this pilot RCT will inform the plan for participant accrual for an RCT of the PEP program, the primary outcome and sample size to be used, and methods to optimize protocol uptake and fidelity. This research will further our understanding of a program that has potential to address the challenging problem of fatigue in the ESRD patient population.

AUTHOR CONTRIBUTIONS

Dr. Janine Farragher and Dr. Brenda Hemmelgarn led the design and writing of the pilot RCT protocol. Dr. Chandra Thomas and Dr. Braden Manns helped with the development of the participant identification plan, and provided advice on other key study issues. Dr. Pietro Ravani and Dr. Meghan Elliott contributed feedback on trial design.

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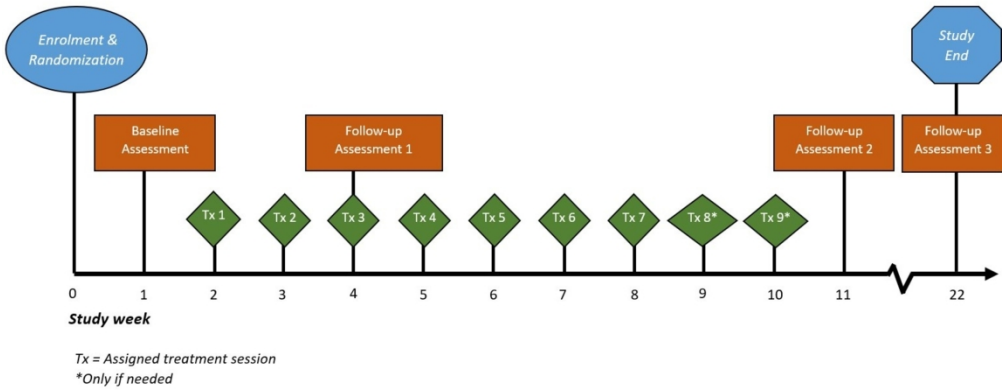
FIGURE LEGENDS

Figure 1: Participant Timeline



Participant Timeline

1276x510mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	4
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 & 21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	10
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Table 4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Table 4
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A (low-risk trial)
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
6Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	4
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

PROTOCOL FOR A PILOT RANDOMIZED CONTROLLED TRIAL OF AN EDUCATIONAL PROGRAM FOR ADULTS ON CHRONIC HEMODIALYSIS WITH FATIGUE (FATIGUE-HD)

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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Fatigue, End stage renal failure < NEPHROLOGY, Rehabilitation medicine < INTERNAL MEDICINE, Randomized Controlled Trial

PROTOCOL FOR A PILOT RANDOMIZED CONTROLLED TRIAL OF AN EDUCATIONAL PROGRAM FOR ADULTS ON CHRONIC HEMODIALYSIS WITH FATIGUE (FATIGUE-HD)

Protocol v2.0 – June 20, 2019

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ABSTRACT

Introduction

Fatigue is a pervasive symptom of end-stage renal disease (ESRD) that is associated with low quality of life, disability and mortality, and has been identified as a top research priority by patients. We developed a personalized, web-supported educational program (the PEP Program) to teach people with ESRD to use energy management to manage fatigue. Preliminary studies have demonstrated positive effects on fatigue and life participation (ie. the ability to participate in valued day-to-day activities), which justifies the need for a randomized controlled trial to better understand the efficacy of the program. The objectives of the pilot RCT are to estimate RCT eligibility, recruitment and attrition rates; inform the primary outcome measure and sample size for the RCT; and evaluate treatment fidelity among program administrators.

Methods and Analysis

A parallel-arm, 1:1 pilot RCT will be conducted at four in-centre hemodialysis units in Calgary, Alberta, Canada. People on hemodialysis who report moderate or severe fatigue on the Fatigue Severity Scale, and meet other study eligibility criteria, will be invited to participate. Consenting participants will be randomized to undergo the 7-9 week "PEP" program or an active control, and followed for 12 weeks after the program concludes. Information on eligibility, recruitment and attrition rates will be collected, and questionnaires assessing fatigue and life participation will be administered pre-intervention, mid-intervention, immediately post-intervention, and 12 weeks post-intervention. Analyses will include calculation of eligibility, recruitment and attrition rates; power considerations for the full-scale RCT; and evaluation of treatment fidelity of program administrators.

Ethics and Dissemination

Risks associated with this study are minor. Patients may experience emotional discomfort while filling out study questionnaires. They will be advised to skip any questions that make them uncomfortable. Potential benefits of participating include any benefit derived from the study intervention, and contributing to research that may benefit people with kidney disease in the future. Trial results will be disseminated via publication in an academic journal and presentation at academic conferences.

ARTICLE SUMMARY

Strengths and Limitations of this Study

- The pilot RCT protocol was developed in accordance with SPIRIT guidelines
- Use of an extensive standardized training protocol for the study intervention to maximize treatment fidelity across program administrators
- Use of an active control condition and blinding of patients and outcome assessors to treatment allocation status, to control for placebo effect
- Exclusion of non-English speaking patients limit its generalizability to non-English ESRD populations
- Non-blinding of treatment administrators may introduce undue bias into study

CLINICAL TRIAL REGISTRY NUMBER

The trial is registered at www.clinicaltrials.gov. Trial identifier: NCT03825770

STUDY INVESTIGATORS

Co-Principal Investigator: Dr. Brenda Hemmelgarn

Co-Principal Investigator: Dr. Janine Farragher

Co-Investigator: Dr. Braden Manns

Co-Investigator: Dr. Chandra Thomas

Co-Investigator: Dr. Pietro Ravani

Co-Investigator: Dr. Meghan Elliott

SPONSORS/SOURCES OF FUNDING

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ACKNOWLEDGEMENTS

None.

KEYWORDS

Fatigue; Renal dialysis; Renal Insufficiency, Chronic; Rehabilitation; Randomized Controlled Trial

DATA STATEMENT

Not applicable (study protocol)

INTRODUCTION

Fatigue is a pervasive symptom of end-stage renal disease (ESRD) experienced by an estimated 7 in 10 people on maintenance dialysis therapy(1). Fatigue has been defined as an "unusual, excessive or whole body tiredness, disproportionate or unrelated to activity or exertion" (2), and is associated with a variety of adverse clinical outcomes, including low quality of life(3,4), hospitalizations (5,6), and mortality (7). Fatigue is viewed as a complex, biopsychosocial symptom of illness (8,9), that can be affected by biological, psychological, behavioral, and treatment-related factors in ESRD (10). Biological factors believed to trigger and perpetuate fatigue in ESRD include anemia, inflammation and uremia(10), while treatment-related factors such as post-dialysis malaise, dialysis adequacy and dialysis modality have also been linked to patient fatigue (10). Psychologically, negative thoughts and beliefs about ESRD and fatigue are purported to result in maladaptive coping responses to fatigue(11), that can worsen the experience of fatigue and might increase the risk of depression and anxiety(12). Patient behaviours such as physical activity levels, sleep patterns, all-or-nothing responses to fatigue, and avoidance of activity are also associated with fatigue in ESRD (10,13). Patients with ESRD have identified fatigue and its negative impact on their life participation (ie. ability to participate in valued day-to-day activities) as top priorities for research (5,14), justifying the need to explore interventions that can reduce fatigue and maximize life participation in this patient population.

The most well-researched approaches for managing fatigue in ESRD are Erythropoetin therapy to target anemia(15) and exercise training to increase physical fitness (16). These approaches, while efficacious for some patients, also have limitations. For example, Erythropoeitin therapy does not address the multiple fatigue mechanisms in ESRD beyond anemia, while exercise training has been challenging to implement and sustain in ESRD clinical practice, due to factors

such as insufficient staff expertise and low patient motivation(17). Cognitive-behavioural therapy for fatigue is an approach targeting unhelpful beliefs and behaviours related to fatigue that has shown promising results in other populations (18,19), and is currently under investigation for people with ESRD(11). Energy management education (EME) is yet another approach to fatigue management, that has also been associated with improvements in other chronic disease populations, such as multiple sclerosis(20–22) and cardiac disease(23,24). The theory behind EME is that fatigue in chronic disease is exacerbated when an individual's energy capacity exceeds their energy expenditure during day-to-day activities, which can consequently interfere with life participation. The objective of EME is therefore to provide practical strategies (eg. prioritizing, using efficient body postures, organizing the home environment) to reduce energy expenditure during everyday life, minimize fatigue and maximize life participation. EME may be well-suited to meet the needs of people with ESRD, as they have been found to have a reduced energy capacity compared to healthy populations (6), and must also expend extra energy on multiple health management tasks associated with dialysis (eg. planning and preparing renal-friendly meals; attending dialysis or performing home dialysis; monitoring fluid intake and blood pressure) in addition to usual daily activities. To date, EME has never been studied in the ESRD population.

We developed a personalized, web-supported EME program (the "PEP" Program), that has been tailored for the ESRD population in several ways. The program is designed specifically to target the impact of fatigue on life participation, in accordance with patient-identified priorities, by using a personalized, goal-focused intervention approach. It is also delivered in a concise, flexible, and web-supported format, to accommodate patients' time restrictions resulting from their dialysis schedules. Preliminary acceptability testing found that the program was both

practical and well-received based on feedback from patient interviews(25), while five single-case studies revealed small to moderate improvements in fatigue and life participation associated with the program in people with ESRD (according to Tau-U statistic of effect-size estimates and in-depth patient interviews) (25). These positive preliminary findings justify a randomized controlled trial (RCT) to more conclusively establish the efficacy of the PEP program.

However, additional information is first needed to design and plan an RCT. First, we need to establish the feasibility of an RCT on the PEP program. Poor recruitment and high attrition rates are common in clinical trials involving ESRD patients, with high illness burden as one possible factor. This could be problematic for a study of an educational program such as the PEP program that will require substantial patient engagement and participation. Second, we need to understand the feasibility of training non-rehabilitation clinicians (eg. nurses) to administer the PEP program for future knowledge translation and program planning purposes, as rehabilitation therapists (who typically administer energy management education programs) are often absent from dialysis units. Finally, we need to collect more data on the effects of the program on possible primary outcomes (fatigue and life participation) to determine the optimal primary outcome measure for an RCT, estimate the sample size for a an RCT, and establish longer-term effects of the PEP program on patient fatigue and life participation.

OBJECTIVES

Primary Objective

1. To estimate the proportion of ESRD patients that are eligible for an RCT of the PEP program, will consent to participate, and will complete all study procedures

Secondary Objectives

1. To identify the fatigue or life participation outcome measure that is most sensitive to change related to the intervention, and estimate the treatment effect size and variability for RCT sample size calculations

2. To explore the in the effects of the PEP program on fatigue and life participation at 3 months post-treatment

3. To examine treatment fidelity to the PEP program among non-rehabilitation clinical staff after participating in a short program training course

METHODS

Trial design

Parallel group, 1:1, pilot randomized controlled trial.

Participant Identification

Participants will be recruited from four in-center hemodialysis units in Calgary, Alberta, Canada. Patients who would be potentially eligible and interested in the study will be identified by clinical staff and approached to assess their interest in the study. Interested patients will undergo a comprehensive informed consent process. Written informed consent will be obtained before any study procedures are undertaken. Consenting participants will undergo full eligibility screening using the study eligibility criteria (Table 1). Consenting and eligible patients will be invited to participate in the study.

Table 1: Study Eligibility Criteria

Inclusion criteria	Exclusion criteria
1. Aged ≥18 years 2. On chronic dialysis therapy for ≥3 months at time of recruitment 3. Clinically and cognitively stable (able to provide informed consent) 4. Scores an avg. of ≥4 on items 5, 7 , 8 and 9 of the Fatigue Severity Scale	1. Inadequate written and verbal English comprehension for study activities 2. Plan in place to discontinue in-center hemodialysis at participating center within 6 months of time of recruitment (due to modality change, relocation, transplantation, or dialysis withdrawal) 3. Resides in a nursing home facility 4. Preclusive visual impairment

Randomization and Concealment

Participants will be allocated equally (1:1) to intervention or control. Permuted blocked randomization with randomly varied block sizes of 2-4 will be performed, and randomization will be stratified by dialysis unit. Participants will be allocated using a computer-generated random number sequence. Randomization will be performed by a research team member who is not involved in other aspects of the study, to maintain allocation concealment.

Blinding

Study participants will be blinded as to which treatment condition is the true treatment under study (intervention or active control). All patient study materials and communications will be left vague, describing the study purpose as being an investigation of an "educational program" for adults with fatigue. Blinding of treatment administrators will not be feasible, given their required level of familiarity with both the treatment and control conditions.

Treatment: The "PEP" Program

Participants randomized to the treatment condition will undergo the "PEP" (Personal Energy Planning) program. The PEP program is a two-part energy management education program, that provides general education about energy management and individualized training to develop personalized energy management strategies. The program is delivered over 7-9 weekly sessions, dependent upon individual patient needs and rates of progress. Sessions are ~20-30 minutes in duration each, and administered either in person or via telephone (based on patient preference). The program is administered by a trained study clinician (occupational therapist or nurse).

Part 1: Participants complete two educational computer modules (20-30 mins each) that explain basic principles related to energy management (eg. energy budgeting; prioritizing; seven key energy-saving strategies), and include activities and exercises to reinforce key concepts. The modules are publicly accessible online (www.pepmodule1.com; www.pepmodule2.com), and can be completed by patients independently (with support provided to access technology, as needed).

Part 2: Participants learn how to apply the energy management principles from Part 1 to accomplish their own life participation goals. First, participants work with a study clinician to identify 3 personal life participation goals (eg. to be able to do the grocery shopping weekly). They then complete a web module (www.pepmodule3.com) that explains a method to identify *personalized* energy management strategies that will facilitate their goals. The method is an adapted version of the Cognitive Orientation to Occupational Performance (CO-OP) intervention(26), which is an evidence-based approach to problem-solving and skill acquisition (27). Key elements of CO-OP include dynamic performance analysis (ie. analyzing where the participant is expending excessive amounts of energy during each goal activity); goal-plan-do-

check (ie., generating energy management "plans", "doing" the plans, and "checking" to see if they work), and guided discovery (a method of questioning and cueing used by the study clinician to enable the participant to discover energy management strategies themselves). Participants spend 5-7 program sessions (15-30 mins each) applying the CO-OP approach with the study clinician to develop and test personalized energy management strategies for accomplishing their goals. The process is continued until an optimal performance solution is found for each goal; or, the program maximum of 9 weekly treatment sessions are reached (whichever comes first). Participants are also given a program workbook to guide them throughout the PEP program.

Control: General Information about Kidney Disease

Participants randomized to the control condition will review information from the Kidney School learning modules (28), during 6-8 individual sessions with a trained study clinician (occupational therapist or nurse). The modules contain general information about managing kidney disease, addressing topics such as diet and heart health. Sessions will take place either in person or via telephone (based on patient preference). Use of this active control condition will minimize the risk of bias associated with patients receiving extra staff attention during the treatment condition.

Treatment Adherence

Study coordinators will monitor and encourage participant adherence to the treatment protocol during weekly visits. All missed or incomplete treatment sessions will be documented.

Staff Training

Treatment administrators will undergo training in the treatment and control protocols, and will each be responsible for providing both treatments. Training for the treatment protocol will consist of three 90 minute sessions, while control protocol training will include one 60 minute

session. A training manual for treatment and control conditions will also be provided to support the administrators. Training materials can be obtained by contacting the study corresponding author.

Concomitant Care

Patients enrolled in the trial will continue to receive and undergo all usual clinical care activities. Changes in clinical care or status during the study that could influence outcomes of fatigue and life participation (eg. exercise regimens; hemoglobin level changes) will be documented.

Data Collection

Demographic and clinical data (Table 2) will be collected for each consenting participant at the time of their first study visit by a trained study assessor, either through chart review or participant interview.

Table 2: Demographic and clinical study variables

Demographic	Clinical
Age	Dialysis vintage
Sex	Comorbidities
Residence type	Most recent hemoglobin
Living status	Most recent albumin
Marital status	ADL independence
Employment	Cognitive function (MiniCOG)
Education	Depression (PHQ-2)

The number of screened patients who meet study inclusion and exclusion criteria; consent to participation and randomization; and complete all study procedures will be documented by study

staff. Follow-up information (including recent hospitalizations, illnesses, dialysis changes, exercise changes, serum hemoglobin and albumin) will be documented at each follow-up visit.

The following questionnaires will be used to measure fatigue and life participation outcomes. These questionnaires were selected based on patient-reported priorities such as minimizing the burden of administration, limiting the recall period, and capturing the impact of fatigue on life participation (5).

Fatigue Severity Scale (FSS)

The FSS(29) asks individuals to rate, on a Likert scale from one to seven, the severity of their fatigue and its impact on their life during the past week. The FSS is a valid, reliable and responsive measure(30,31) that has previously been used in the dialysis population(12).

Fatigue Management Questionnaire (FMQ)

The FMQ asks participants to rate various aspects of their fatigue management (eg. competence, satisfaction, self-efficacy) on a Likert Scale of 1-10. The questionnaire was created for this study to fill a gap in assessments that measure life participation and self-efficacy specifically related to fatigue management.

Modified Fatigue Impact Scale (MFIS)

The MFIS(32) is a 21-item Likert-based scale that assesses the effects of fatigue on physical, cognitive, and psychosocial functioning. The Fatigue Impact Scale has frequently been used as an outcome measure in energy management education studies.

Reintegration to Normal Living Index (RNLI)

The RNLI(33) assesses the degree to which individuals who have experienced traumatic or incapacitating illness achieve reintegration into normal social activities, using 11 declarative

statements that are accompanied by a visual analogue scale (VAS). The RNLI has been found to have strong validity and reliability in multiple disease populations(34).

Canadian Occupational Performance Measure (COPM)

The COPM(35) is designed to capture a client's perception of his/her performance in three priority tasks of everyday living. It asks individuals to rate, on a 10-point Likert scale, the importance of three self-chosen priority activities; their current perceived performance on the priority activities; and their satisfaction with that performance. The COPM has been found to be a valid, reliable, clinically useful and responsive outcome measure in multiple disease populations(36).

The fatigue and life participation questionnaires will be administered at four timepoints (Figure 1) (except the COPM, which will not be administered at baseline):

1. Pre-intervention baseline
2. Post-Part 1 of the PEP program (just prior to commencing Part 2, session 1)
3. Post-Part 2 of the PEP program (one week after the final study visit)
4. 12 weeks after the final study visit

Questionnaires will be completed before, during, or after a dialysis session, according to participant preference. The timing and location of questionnaire completion will be kept consistent across assessment timepoints for each participant.

All treatment sessions (excluding computer modules) will be audio-recorded on an audio recording device. Two sessions per participant randomized to the treatment condition will then be randomly selected and used to evaluate treatment fidelity of the program administrators, according to the CO-OP fidelity checklist. The checklist includes 26 items, each scored on a

scale of 0-5, that measure the extent of use of various key elements of the treatment approach by the treatment administrator.

Data Management & Confidentiality

Study data will be recorded onto standardized paper study forms at the time of collection. Data will be anonymized by assigning each participant an unidentifiable study ID number at the time of enrolment that will be used to identify them for all study materials. Paper data forms will immediately be filed and stored in a locked office area, and signed study consent forms will be filed and stored separately from data forms to maintain participant anonymity.

Study data will subsequently be entered into a secure database by a research assistant. The database will be password protected and stored on a secure server, with access restricted to authorized users of the server. Range checks for data values will be performed after data entry, to promote data quality.

Audio recordings of study sessions will also be transferred onto a secure server, and deleted from their original recording device at the time of transfer. A sample of the audio recordings will subsequently be transcribed into text by the team transcriptionist and stored on the secure server. Data files and documents will be destroyed 7 years after the project is closed.

Protocol Deviations and Amendments

Protocol deviations are reported in Table 3. Any mid-study protocol modifications will be submitted to co-investigators and REB for approval and communicated to study participants and the trial registry once approved.

Table 3: Protocol Deviations

Protocol Deviations
a. Failure to initiate treatment within 2 weeks of study screening & enrolment b. Missed ≥3 consecutive treatment or control sessions, leading to discontinuation of assigned treatment condition (but not withdrawal from study) c. Missed ≥2 consecutive study assessment visits, leading to non-completion of an assessment package (but not withdrawal from study) d. Participants switch ESRD treatment modality during the course of the study e. Participants are hospitalized overnight during the course of the study f. Dropouts and their causes (eg. withdrawal of consent* or transfer to another centre)

Missed Study Treatment or Assessment Appointment

Missed study sessions will be addressed as outlined in Table 4. The study treatment and assessment schedule has been designed with flexibility to accommodate the frequent changes in health status and fatigue levels experienced by this population, which may cause occasional missed study appointments.

Table 4: Protocol for Missed Study Sessions

Missed Session Details	Response
Participant misses 1-2 consecutive weekly treatment sessions	-Missed appointment(s) will be documented

	-The scheduled treatment session will be delayed until the next weekly session -Dates of remaining assessment and treatment sessions will be delayed accordingly
Participant misses 3 or more consecutive weekly treatment sessions	-Missed appointments will be documented -Treatment protocol will be discontinued -Treatment discontinuation will be recorded as a Protocol Deviation -Assessment schedule will carry on as planned, regardless of missed treatment sessions
Participant misses scheduled assessment appointment date and does not complete it during the week of the scheduled date, but completes it the following week	-Missed appointment date will be documented -The scheduled assessment will be delayed to the following week -Dates of remaining treatment and assessment sessions will be delayed accordingly
Participant misses scheduled assessment appointment by >1 week	-Missed appointment will be documented -Missed assessment will be recorded as a Protocol Deviation -No additional attempts will be made to complete the missed assessment

Data Analysis

Demographic and clinical data will be reported as means and standard deviations for continuous parametric data; medians and ranges for continuous nonparametric data; and frequencies and percentages for categorical data.

The proportion of patients meeting each of the feasibility endpoints (eligibility, recruitment and attrition rates), with accompanying 95% confidence intervals, will be calculated.

Assuming a normal distribution, standardized effect sizes for each fatigue & disability outcome measure will be calculated for both immediate post-intervention and three months post-intervention, as follows:

$$\text{Cohen's D} = \frac{\text{Mean pre-post change (treatment)} - \text{Mean pre-post change (control)}}{\text{Standard deviation (pooled)}}$$

These data will be analyzed using intention-to treat analysis. Sample size calculations for the RCT will be made using the treatment effect size and variance estimates from the immediate post-intervention change data for the selected outcome measure. Missing follow-up data will be addressed using pairwise deletion.

The treatment fidelity of treatment administrators will be analyzed by calculating an average score out of 5 on the CO-OP fidelity checklist, for one treatment session per participant randomized to the treatment condition.

SAMPLE SIZE AND FEASIBILITY

A sample size of 40 patients (20 per treatment arm) was chosen to provide a sufficiently precise estimate of the treatment effect for RCT sample size calculations(37), given 80% power, a small-medium effect size on fatigue/life participation, and an anticipated attrition rate of ≤20%. There are approximately 425 prevalent patients on hemodialysis in total at the four participating clinical sites. Based on conservative estimates of 40% eligibility and 30% recruitment rates, the patient pool will be adequate to achieve the target sample size for the pilot RCT.

PATIENT AND PUBLIC INVOLVEMENT

Patients have been involved, both directly and indirectly, in multiple aspects of this research project. The intervention under study was developed in response to results of patient engagement research, which identified a need to further investigate fatigue management in renal disease(14). Two patients were involved as key informants in the development of the intervention under study, providing consultation and feedback on the first intervention prototype through a series of individual interviews that led to several program modifications (eg. clarification of key content; simplification of design features). Two patients were also consulted about the control condition to be used in this study, and their feedback led to modifications such as individualization of the content material for specific patient interests and needs. Our current study team includes a patient partner who will be consulted about patient-related issues that arise during the study, the interpretation of results, and strategies to optimize dissemination and uptake.

ETHICAL CONSIDERATIONS

Risks and Benefits

As part of their baseline assessment, participants will complete the PHQ-2 depression screening assessment. This assessment may identify individuals who have, or are at risk for, clinical depression. Any individual who scores >2 on the PHQ-2 will be offered connection to support services, such as referral to their clinical social worker, or to a local counselling centre. Study participants will also have to complete several study questionnaires, and participate in PEP program treatment sessions. There is a risk that patients may experience short-term fatigue, or, uncomfortable or unpleasant emotions in response to some of the questions in the study

questionnaires. Participants will therefore be advised that they can skip any questions or study procedures that make them uncomfortable.

Direct benefits of participating are those which may be gained from completing the study intervention, such as improved fatigue management, improved knowledge about kidney disease, and/or and increased staff attention. Indirect benefits include the potential that others with kidney disease may benefit from the study findings in the future.

Data Safety and Monitoring Board (DSMB)

As the proposed study is small and its risks to participants are low, a DSMB is not needed. Monitoring for potential risks (eg. fatigue, discomfort) will be performed by those interacting directly with the patient during the study (the study clinicians and assessor). If any unexpected concerns arise that cannot be immediately mitigated, the concerns will be brought forth to the PIs for further discussion and decision-making.

Research Ethics Approval

Ethics approval for the study has been obtained from the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary.

DISSEMINATION PLAN

Trial results will be disseminated to patients with a summary sheet that will outline the trial findings in lay language. Results will be disseminated to healthcare professionals and researchers via publication in an academic journal and presentation at academic conferences.

DISCUSSION

Fatigue is a common and disabling symptom of end-stage renal disease(1,4–6), that has traditionally been challenging to mitigate due to its complex and nonspecific etiology. Results from patient-reported outcome and engagement studies have highlighted the need to continue to explore new fatigue management interventions for people with ESRD(5,14). Energy management education (EME) is an approach that has been associated with positive fatigue-related outcomes in other chronic disease populations. For example, in people with MS, RCTs have found that EME reduces patient fatigue and its impact on physical, cognitive and psychosocial functioning, and improves self-efficacy(20–22,38,39). Earlier-phase studies in acquired brain injury(40), cardiac disease(23,24), and post-polio(41) have similarly shown positive effects on fatigue and other related, high-priority outcomes, such as life participation (23,40). Furthermore, single-case studies conducted in a small sample of ESRD patients have generated promising findings regarding the effects of the PEP program on fatigue and life participation in people on chronic dialysis (25), suggesting this approach has potential to fill an important gap in ESRD care. However, studies in ESRD have thus far lacked important design elements, such as blinding, randomization, and sample representativeness, leaving the true potential of the PEP program unclear.

This proposed pilot RCT will provide several pieces of feasibility information to help plan an RCT, that can more conclusively establish the efficacy of the PEP program in people with ESRD. It will provide more accurate preliminary estimates of program effect sizes than are currently available, enabling greater precision in RCT power and sample size calculations. It will also provide estimates of eligibility, recruitment and attrition rates, which will help to ensure that adequate numbers of patients are approached for the RCT. Finally, it will help us to maximize

fidelity to the treatment protocol in the RCT by providing information on the effectiveness of the current staff training program, and the potential need to involve rehabilitation specialists in future program research and implementation. These will all be necessary factors to ensure successful future implementation of an RCT.

The proposed pilot RCT has a number of strengths. The program under investigation (the PEP program) has been tailored specifically to meet the needs of the ESRD population: it is designed to facilitate participation in meaningful activities, which is a high priority for ESRD patients, and is delivered in a flexible format to accommodate the dialysis schedule. Patients have also been consulted and provided input at several stages of intervention development and testing. The study protocol was developed using the SPIRIT guidelines for a pilot RCT protocol, increasing the likelihood that important study design elements have been addressed. We have also developed a standardized training and administration protocol for the PEP program, that we anticipate will maximize treatment fidelity and consistency across program administrators. An active control condition to blind patients to their treatment allocation status will further increase the confidence in our study findings, by controlling for the placebo effect.

Our study also has limitations. First, we are excluding non-English speaking patients from the study, which limits its generalizability to non-English-speaking ESRD populations. However, the findings from this study may help to justify developing program materials in alternative languages that are accessible to a wider range of renal patients. We are also excluding patients outside of the in-center hemodialysis population who also experience a high burden of fatigue (eg. predialysis patients, peritoneal dialysis patients, home hemodialysis patients). This study

should be viewed as an important first step in establishing the potential for the PEP program, that can lay the groundwork for future research into energy management education in other renal populations. Finally, we are unable to blind treatment administrators to treatment allocation, due to our inability to conceal which study condition is the treatment condition. We perceive blinding to be unfeasible because treatment administrators would be able to identify the treatment condition, based on inequities between the two conditions in the amount of content dedicated to fatigue and the length of time spent on staff training. The infeasibility of blinding is a well-recognized limitation of trials studying psychosocial or behavioural interventions that are not easily matched with an equivalent control.

In conclusion, the findings from this pilot RCT will further our understanding of a program that has potential to address the challenging problem of fatigue in the ESRD patient population.

TRIAL STATUS

The study started recruitment at the end of February 2019. Recruitment will continue until August 2019. Data collection will conclude in January 2020.

AUTHOR CONTRIBUTIONS

Dr. Janine Farragher and Dr. Brenda Hemmelgarn led the design and writing of the pilot RCT protocol. Dr. Chandra Thomas and Dr. Braden Manns helped with the development of the participant identification plan, and provided advice on other key study issues. Dr. Pietro Ravani and Dr. Meghan Elliott contributed feedback on trial design.

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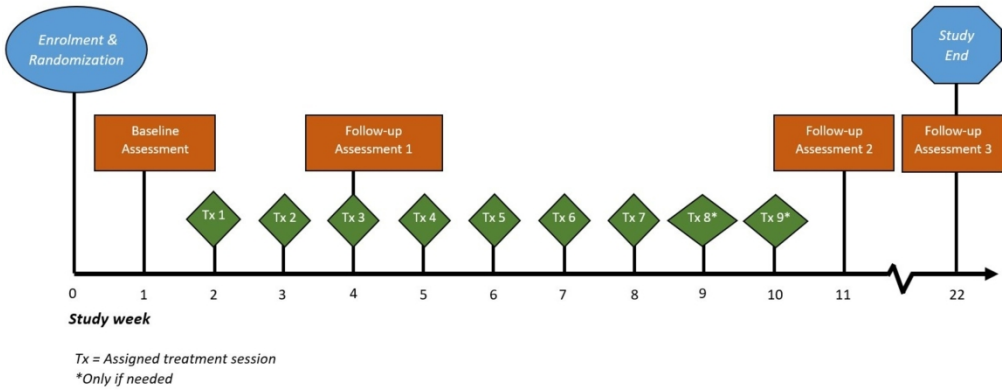
FIGURE LEGENDS

Figure 1: Participant Timeline



Participant Timeline

1276x510mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	4
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 & 21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	10
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Table 4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Table 4
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A (low-risk trial)
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
6Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	4
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

PROTOCOL FOR A PILOT RANDOMIZED CONTROLLED TRIAL OF AN EDUCATIONAL PROGRAM FOR ADULTS ON CHRONIC HEMODIALYSIS WITH FATIGUE (FATIGUE-HD)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030333.R2
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Complete List of Authors:	Farragher, Janine; University of Calgary, Community Health Sciences Thomas, Chandra; University of Calgary, Medicine Ravani, P; University of Calgary, Medicine Manns, Braden; Foothills Medical Centre Elliott, Meghan; University of Calgary, Medicine Hemmelgarn, Brenda; University of Calgary
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Fatigue, End stage renal failure < NEPHROLOGY, Rehabilitation medicine < INTERNAL MEDICINE, Randomized Controlled Trial

PROTOCOL FOR A PILOT RANDOMIZED CONTROLLED TRIAL OF AN EDUCATIONAL PROGRAM FOR ADULTS ON CHRONIC HEMODIALYSIS WITH FATIGUE (FATIGUE-HD)

Protocol v3.0 – June 30, 2019

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Word Count: 4169

ABSTRACT

Introduction

Fatigue is a pervasive symptom of end-stage renal disease (ESRD) that is associated with low quality of life, disability and mortality, and has been identified as a top research priority by patients. We developed a personalized, web-supported educational program (the PEP Program) to teach people with ESRD to use energy management to manage fatigue. Preliminary studies have demonstrated positive effects on fatigue and life participation (ie. the ability to participate in valued day-to-day activities), which justifies the need for a randomized controlled trial to better understand the efficacy of the program. The objectives of the pilot RCT are to estimate RCT eligibility, recruitment and attrition rates; inform the primary outcome measure and sample size for the RCT; and evaluate treatment fidelity among program administrators.

Methods and Analysis

A parallel-arm, 1:1 pilot RCT will be conducted at four in-centre hemodialysis units in Calgary, Alberta, Canada. People on hemodialysis who report moderate or severe fatigue on the Fatigue Severity Scale, and meet other study eligibility criteria, will be invited to participate. Consenting participants will be randomized to undergo the 7-9 week "PEP" program or an active control, and followed for 12 weeks after the program concludes. Information on eligibility, recruitment and attrition rates will be collected, and questionnaires assessing fatigue and life participation will be administered pre-intervention, mid-intervention, immediately post-intervention, and 12 weeks post-intervention. Analyses will include calculation of eligibility, recruitment and attrition rates; power considerations for the full-scale RCT; and evaluation of treatment fidelity of program administrators.

Ethics and Dissemination

Risks associated with this study are minor. Patients may experience emotional discomfort while filling out study questionnaires. They will be advised to skip any questions that make them uncomfortable. Potential benefits of participating include any benefit derived from the study intervention, and contributing to research that may benefit people with kidney disease in the future. Trial results will be disseminated via publication in an academic journal and presentation at academic conferences. The study has been approved by the Conjoint Health Research Ethics Board at the University of Calgary (ID #18-1657).

ARTICLE SUMMARY

Strengths and Limitations of this Study

- The pilot RCT protocol was developed in accordance with SPIRIT guidelines
- Use of an extensive standardized training protocol for the study intervention to maximize treatment fidelity across program administrators
- Use of an active control condition and blinding of patients and outcome assessors to treatment allocation status, to control for placebo effect
- Exclusion of non-English speaking patients limit its generalizability to non-English ESRD populations
- Non-blinding of treatment administrators may introduce undue bias into study

CLINICAL TRIAL REGISTRY NUMBER

The trial is registered at www.clinicaltrials.gov. Trial identifier: NCT03825770

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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None.

KEYWORDS

Fatigue; Renal dialysis; Renal Insufficiency, Chronic; Rehabilitation; Randomized Controlled Trial

DATA STATEMENT

Not applicable (study protocol)

INTRODUCTION

Fatigue is a pervasive symptom of end-stage renal disease (ESRD) experienced by an estimated 7 in 10 people on maintenance dialysis therapy(1). Fatigue has been defined as an "unusual, excessive or whole body tiredness, disproportionate or unrelated to activity or exertion" (2), and is associated with a variety of adverse clinical outcomes, including low quality of life(3,4), hospitalizations (5,6), and mortality (7). Fatigue is viewed as a complex, biopsychosocial symptom of illness (8,9), that can be affected by biological, psychological, behavioral, and treatment-related factors in ESRD (10). Biological factors believed to trigger and perpetuate fatigue in ESRD include anemia, inflammation and uremia(10), while treatment-related factors such as post-dialysis malaise, dialysis adequacy and dialysis modality have also been linked to patient fatigue (10). Psychologically, negative thoughts and beliefs about ESRD and fatigue are purported to result in maladaptive coping responses to fatigue(11), that can worsen the experience of fatigue and might increase the risk of depression and anxiety(12). Patient behaviours such as physical activity levels, sleep patterns, all-or-nothing responses to fatigue, and avoidance of activity are also associated with fatigue in ESRD (10,13). Patients with ESRD have identified fatigue and its negative impact on their life participation (ie. ability to participate in valued day-to-day activities) as top priorities for research (5,14), justifying the need to explore interventions that can reduce fatigue and maximize life participation in this patient population.

The most well-researched approaches for managing fatigue in ESRD are Erythropoetin therapy to target anemia(15) and exercise training to increase physical fitness (16). These approaches, while efficacious for some patients, also have limitations. For example, Erythropoeitin therapy does not address the multiple fatigue mechanisms in ESRD beyond anemia, while exercise training has been challenging to implement and sustain in ESRD clinical practice, due to factors such as insufficient staff expertise and low patient motivation(17). Cognitive-behavioural therapy for fatigue is an approach targeting unhelpful beliefs and behaviours related to fatigue that has shown promising results in other populations (18,19), and is currently under investigation for people with ESRD(11). Energy management education (EME) is yet another approach to fatigue management, that has also been associated with improvements in other chronic disease populations, such as multiple sclerosis(20–22) and cardiac disease(23,24). The theory behind EME is that fatigue in chronic disease is exacerbated when an individual's energy capacity exceeds their energy expenditure during day-to-day activities, which can consequently interfere with life participation. The objective of EME is therefore to provide practical strategies (eg. prioritizing, using efficient body postures, organizing the home environment) to reduce energy expenditure during everyday life, minimize fatigue and maximize life participation. EME may be well-suited to meet the needs of people with ESRD, as they have been found to have a reduced energy capacity compared to healthy populations (6), and must also expend extra energy on multiple health management tasks associated with dialysis (eg. planning and preparing renal-friendly meals; attending dialysis or performing home dialysis; monitoring fluid intake and blood pressure) in addition to usual daily activities. To date, EME has never been studied in the ESRD population.

We developed a personalized, web-supported EME program (the "PEP" Program), that has been tailored for the ESRD population in several ways. The program is designed specifically to target the impact of fatigue on life participation, in accordance with patient-identified priorities, by using a personalized, goal-focused intervention approach. It is also delivered in a concise, flexible, and web-supported format with minimal homework, to accommodate patients' time restrictions resulting from their dialysis schedules. Preliminary acceptability testing found that the program was both practical and well-received based on feedback from patient interviews(25), while five single-case studies revealed small to moderate improvements in fatigue and life participation associated with the program in people with ESRD (according to Tau-U statistic of effect-size estimates and in-depth patient interviews) (25). These positive preliminary findings justify a randomized controlled trial (RCT) to more conclusively establish the efficacy of the PEP program.

However, additional information is first needed to design and plan an RCT. First, we need to establish the feasibility of an RCT on the PEP program. Poor recruitment and high attrition rates are common in clinical trials involving ESRD patients, with high illness burden as one possible factor. This could be problematic for a study of an educational program such as the PEP program that will require substantial patient engagement and participation. Second, we need to understand the feasibility of training non-rehabilitation clinicians (eg. nurses) to administer the PEP program for future knowledge translation and program planning purposes, as rehabilitation therapists (who typically administer energy management education programs) are often absent from dialysis units. Finally, we need to collect more data on the effects of the program on possible primary outcomes (fatigue and life participation) to determine the optimal primary outcome

measure for an RCT, estimate the sample size for a an RCT, and establish longer-term effects of the PEP program on patient fatigue and life participation.

OBJECTIVES

Primary Objective

1. To estimate the proportion of ESRD patients that are eligible for an RCT of the PEP program, will consent to participate, and will complete all study procedures

Secondary Objectives

1. To identify the fatigue or life participation outcome measure that is most sensitive to change related to the intervention, and estimate the treatment effect size and variability for RCT sample size calculations

2. To explore the in the effects of the PEP program on fatigue and life participation at 3 months post-treatment

3. To examine treatment fidelity to the PEP program among non-rehabilitation clinical staff after participating in a short program training course

METHODS

Trial design

Parallel group, 1:1, pilot randomized controlled trial.

Participant Identification

Participants will be recruited from four in-center hemodialysis units in Calgary, Alberta, Canada. Patients who would be potentially eligible and interested in the study will be identified by

clinical staff and approached to assess their interest in the study. Interested patients will undergo a comprehensive informed consent process. Written informed consent will be obtained before any study procedures are undertaken. Consenting participants will undergo full eligibility screening, using the study eligibility criteria (Table 1). Items 5, 7, 8 and 9 of the Fatigue Severity Scale are being used to identify eligible patients because these items specifically ask about the impact of fatigue on life participation, which is the intended focus of the intervention. Consenting and eligible patients will be invited to participate in the study.

Table 1: Study Eligibility Criteria

Inclusion criteria	Exclusion criteria
1. Aged ≥18 years 2. On chronic dialysis therapy for ≥3 months at time of recruitment 3. Clinically and cognitively stable (able to provide informed consent) 4. Scores an avg. of ≥4 on items 5, 7 , 8 and 9 of the Fatigue Severity Scale	1. Inadequate written and verbal English comprehension for study activities 2. Plan in place to discontinue in-center hemodialysis at participating center within 6 months of time of recruitment (due to modality change, relocation, transplantation, or dialysis withdrawal) 3. Resides in a nursing home facility 4. Preclusive visual impairment

Randomization and Concealment

Participants will be allocated equally (1:1) to intervention or control. Permuted blocked randomization with randomly varied block sizes of 2-4 will be performed, and randomization will be stratified by dialysis unit. Participants will be allocated using a computer-generated random number sequence. Randomization will be performed by a research team member who is not involved in other aspects of the study, to maintain allocation concealment.

Blinding

Study participants will be blinded as to which treatment condition is the true treatment under

study (intervention or active control). All patient study materials and communications will be left vague, describing the study purpose as being an investigation of an "educational program" for adults with fatigue. Blinding of treatment administrators will not be feasible, given their required level of familiarity with both the treatment and control conditions.

Treatment: The "PEP" Program

Participants randomized to the treatment condition will undergo the "PEP" (Personal Energy Planning) program. The PEP program is a two-part energy management education program, that provides general education about energy management and individualized training to develop personalized energy management strategies. The program is delivered over 7-9 weekly sessions, dependent upon individual patient needs and rates of progress. Sessions are ~20-30 minutes in duration each, and administered either in person or via telephone (based on patient preference). The program is administered by a trained study clinician (occupational therapist or nurse).

Part 1: Participants complete two educational computer modules (20-30 mins each) that explain basic principles related to energy management (eg. energy budgeting; prioritizing; seven key energy-saving strategies), and include activities and exercises to reinforce key concepts. The modules are publicly accessible online (www.pepmodule1.com; www.pepmodule2.com), and can be completed by patients independently (with support provided to access technology, as needed).

Part 2: Participants learn how to apply the energy management principles from Part 1 to accomplish their own life participation goals. First, participants work with a study clinician to identify 3 personal life participation goals (eg. to be able to do the grocery shopping weekly). They then complete a web module (www.pepmodule3.com) that explains a method to identify *personalized* energy management strategies that will facilitate their goals. The method is an

adapted version of the Cognitive Orientation to Occupational Performance (CO-OP) intervention(26), which is an evidence-based approach to problem-solving and skill acquisition (27). Key elements of CO-OP include dynamic performance analysis (ie. analyzing where the participant is expending excessive amounts of energy during each goal activity); goal-plan-do-check (ie., generating energy management "plans", "doing" the plans, and "checking" to see if they work), and guided discovery (a method of questioning and cueing used by the study clinician to enable the participant to discover energy management strategies themselves). Participants spend 5-7 program sessions (15-30 mins each) applying the CO-OP approach with the study clinician to develop and test personalized energy management strategies for accomplishing their goals. The process is continued until an optimal performance solution is found for each goal; or, the program maximum of 9 weekly treatment sessions are reached (whichever comes first). Participants are also given a program workbook to guide them throughout the PEP program.

Control: General Information about Kidney Disease

Participants randomized to the control condition will review information from the Kidney School learning modules (28), during 6-8 individual sessions with a trained study clinician (occupational therapist or nurse). The modules contain general information about managing kidney disease, addressing topics such as diet and heart health. Sessions will take place either in person or via telephone (based on patient preference). Use of this active control condition will minimize the risk of bias associated with patients receiving extra staff attention during the treatment condition.

Treatment Adherence

Study coordinators will monitor and encourage participant adherence to the treatment protocol during weekly visits. All missed or incomplete treatment sessions will be documented.

Staff Training

Treatment administrators will undergo training in the treatment and control protocols, and will each be responsible for providing both treatments. Training for the treatment protocol will consist of three 90 minute sessions, while control protocol training will include one 60 minute session. A training manual for treatment and control conditions will also be provided to support the administrators. Training materials can be obtained by contacting the study corresponding author.

Concomitant Care

Patients enrolled in the trial will continue to receive and undergo all usual clinical care activities. Changes in clinical care or status during the study that could influence outcomes of fatigue and life participation (eg. exercise regimens; hemoglobin level changes) will be documented.

Data Collection

Demographic and clinical data (Table 2) will be collected for each consenting participant at the time of their first study visit by a trained study assessor, either through chart review or participant interview.

Table 2: Demographic and clinical study variables

Demographic	Clinical
Age	Dialysis vintage
Sex	Comorbidities
Residence type	Most recent hemoglobin
Living status	Most recent albumin
Marital status	ADL independence
Employment	Cognitive function (MiniCOG)
Education	Depression (PHQ-2)

The number of screened patients who meet study inclusion and exclusion criteria; consent to participation and randomization; and complete all study procedures will be documented by study staff. Follow-up information (including recent hospitalizations, illnesses, dialysis changes, exercise changes, serum hemoglobin and albumin) will be documented at each follow-up visit.

The following questionnaires will be used to measure fatigue and life participation outcomes. These questionnaires were selected based on patient-reported priorities such as minimizing the burden of administration, limiting the recall period, and capturing the impact of fatigue on life participation (5).

Fatigue Severity Scale (FSS)

The FSS(29) asks individuals to rate, on a Likert scale from one to seven, the severity of their fatigue and its impact on their life during the past week. The FSS is a valid, reliable and responsive measure(30,31) that has previously been used in the dialysis population(12).

Fatigue Management Questionnaire (FMQ)

The FMQ asks participants to rate various aspects of their fatigue management (eg. competence, satisfaction, self-efficacy) on a Likert Scale of 1-10. The questionnaire was created for this study to fill a gap in assessments that measure life participation and self-efficacy specifically related to fatigue management.

Modified Fatigue Impact Scale (MFIS)

The MFIS(32) is a 21-item Likert-based scale that assesses the effects of fatigue on physical, cognitive, and psychosocial functioning. The Fatigue Impact Scale has frequently been used as an outcome measure in energy management education studies.

Reintegration to Normal Living Index (RNLI)

The RNLI(33) assesses the degree to which individuals who have experienced traumatic or incapacitating illness achieve reintegration into normal social activities, using 11 declarative statements that are accompanied by a visual analogue scale (VAS). The RNLI has been found to have strong validity and reliability in multiple disease populations(34).

Canadian Occupational Performance Measure (COPM)

The COPM(35) is designed to capture a client's perception of his/her performance in three priority tasks of everyday living. It asks individuals to rate, on a 10-point Likert scale, the importance of three self-chosen priority activities; their current perceived performance on the priority activities; and their satisfaction with that performance. The COPM has been found to be a valid, reliable, clinically useful and responsive outcome measure in multiple disease populations(36).

The fatigue and life participation questionnaires will be administered at four timepoints (Figure 1) (except the COPM, which will not be administered at baseline):

1. Pre-intervention baseline
2. Post-Part 1 of the PEP program (just prior to commencing Part 2, session 1)
3. Post-Part 2 of the PEP program (one week after the final study visit)
4. 12 weeks after the final study visit

Questionnaires will be completed before, during, or after a dialysis session, according to participant preference. The timing and location of questionnaire completion will be kept consistent across assessment timepoints for each participant.

All treatment sessions (excluding computer modules) will be audio-recorded on an audio recording device. Two sessions per participant randomized to the treatment condition will then be randomly selected and used to evaluate treatment fidelity of the program administrators, according to the CO-OP fidelity checklist. The checklist includes 26 items, each scored on a scale of 0-5, that measure the extent of use of various key elements of the treatment approach by the treatment administrator.

Data Management & Confidentiality

Study data will be recorded onto standardized paper study forms at the time of collection. Data will be anonymized by assigning each participant an unidentifiable study ID number at the time of enrolment that will be used to identify them for all study materials. Paper data forms will immediately be filed and stored in a locked office area, and signed study consent forms will be filed and stored separately from data forms to maintain participant anonymity.

Study data will subsequently be entered into a secure database by a research assistant. The database will be password protected and stored on a secure server, with access restricted to authorized users of the server. Range checks for data values will be performed after data entry, to promote data quality.

Audio recordings of study sessions will also be transferred onto a secure server, and deleted from their original recording device at the time of transfer. A sample of the audio recordings will subsequently be transcribed into text by the team transcriptionist and stored on the secure server. Data files and documents will be destroyed 7 years after the project is closed.

Protocol Deviations and Amendments

Protocol deviations are reported in Table 3. Any mid-study protocol modifications will be

submitted to co-investigators and REB for approval and communicated to study participants and the trial registry once approved.

Table 3: Protocol Deviations

Protocol Deviations
a. Failure to initiate treatment within 2 weeks of study screening & enrolment b. Missed ≥3 consecutive treatment or control sessions, leading to discontinuation of assigned treatment condition (but not withdrawal from study) c. Missed ≥2 consecutive study assessment visits, leading to non-completion of an assessment package (but not withdrawal from study) d. Participants switch ESRD treatment modality during the course of the study e. Participants are hospitalized overnight during the course of the study f. Dropouts and their causes (eg. withdrawal of consent* or transfer to another centre)

Missed Study Treatment or Assessment Appointment

Missed study sessions will be addressed as outlined in Table 4. The study treatment and assessment schedule has been designed with flexibility to accommodate the frequent changes in health status and fatigue levels experienced by this population, which may cause occasional missed study appointments.

Table 4: Protocol for Missed Study Sessions

Missed Session Details	Response
Participant misses **1-2** consecutive weekly treatment sessions	-Missed appointment(s) will be documented -The scheduled treatment session will be delayed until the next weekly session -Dates of remaining assessment and treatment sessions will be delayed accordingly
Participant misses **3 or more** consecutive weekly treatment sessions	-Missed appointments will be documented -Treatment protocol will be discontinued -Treatment discontinuation will be recorded as a Protocol Deviation

	-Assessment schedule will carry on as planned, regardless of missed treatment sessions
Participant misses scheduled assessment appointment date and does not complete it during the week of the scheduled date, but completes it the following week	-Missed appointment date will be documented -The scheduled assessment will be delayed to the following week -Dates of remaining treatment and assessment sessions will be delayed accordingly
Participant misses scheduled assessment appointment by **>1 week**	-Missed appointment will be documented -Missed assessment will be recorded as a Protocol Deviation -No additional attempts will be made to complete the missed assessment

Data Analysis

Demographic and clinical data will be reported as means and standard deviations for continuous parametric data; medians and ranges for continuous nonparametric data; and frequencies and percentages for categorical data.

The proportion of patients meeting each of the feasibility endpoints (eligibility, recruitment and attrition rates), with accompanying 95% confidence intervals, will be calculated.

Assuming a normal distribution, standardized effect sizes for each fatigue & disability outcome measure will be calculated for both immediate post-intervention and three months post-intervention, as follows:

$$\text{Cohen's D} = \frac{\text{Mean pre-post change (treatment)} - \text{Mean pre-post change (control)}}{\text{Standard deviation (pooled)}}$$

These data will be analyzed using intention-to treat analysis. Sample size calculations for the RCT will be made using the treatment effect size and variance estimates from the immediate

post-intervention change data for the selected outcome measure. Missing follow-up data will be addressed using pairwise deletion.

The treatment fidelity of treatment administrators will be analyzed by calculating an average score out of 5 on the CO-OP fidelity checklist, for one treatment session per participant randomized to the treatment condition.

SAMPLE SIZE AND FEASIBILITY

A sample size of 40 patients (20 per treatment arm) was chosen based on the recommendations of Whitehead et al. (37). They suggest this sample size will provide a sufficiently precise estimate of the treatment effect to minimize the sample needed for a future RCT, assuming 80% power, a small-medium effect size (which is expected based on our preliminary data (25)), and an attrition rate of no more than ≤25%.

There are approximately 425 prevalent patients on hemodialysis in total at the four participating clinical sites. We project that approximately half (212 patients) will be identified as potential participants with fatigue, based on preliminary symptom screening data from the sites. Given that this is a high-priority research area among dialysis patients, we conservatively estimate that at least 25% (56 patients) of patients with fatigue will agree to participate. Furthermore, we expect no more than 25% of patients will subsequently be excluded during eligibility screening. This will enable us to achieve the target sample size of 40 patients.

PATIENT AND PUBLIC INVOLVEMENT

Patients have been involved, both directly and indirectly, in multiple aspects of this research project. The intervention under study was developed in response to results of patient engagement

research, which identified a need to further investigate fatigue management in renal disease(14). Two patients were involved as key informants in the development of the intervention under study, providing consultation and feedback on the first intervention prototype through a series of individual interviews that led to several program modifications (eg. clarification of key content; simplification of design features). Two patients were also consulted about the control condition to be used in this study, and their feedback led to modifications such as individualization of the content material for specific patient interests and needs. Our current study team includes a patient partner who will be consulted about patient-related issues that arise during the study, the interpretation of results, and strategies to optimize dissemination and uptake.

ETHICAL CONSIDERATIONS

Risks and Benefits

As part of their baseline assessment, participants will complete the PHQ-2 depression screening assessment. This assessment may identify individuals who have, or are at risk for, clinical depression. Any individual who scores >2 on the PHQ-2 will be offered connection to support services, such as referral to their clinical social worker, or to a local counselling centre. Study participants will also have to complete several study questionnaires, and participate in PEP program treatment sessions. There is a risk that patients may experience short-term fatigue, or, uncomfortable or unpleasant emotions in response to some of the questions in the study questionnaires. Participants will therefore be advised that they can skip any questions or study procedures that make them uncomfortable.

Direct benefits of participating are those which may be gained from completing the study intervention, such as improved fatigue management, improved knowledge about kidney disease,

and/or and increased staff attention. Indirect benefits include the potential that others with kidney disease may benefit from the study findings in the future.

Data Safety and Monitoring Board (DSMB)

As the proposed study is small and its risks to participants are low, a DSMB is not needed. Monitoring for potential risks (eg. fatigue, discomfort) will be performed by those interacting directly with the patient during the study (the study clinicians and assessor). If any unexpected concerns arise that cannot be immediately mitigated, the concerns will be brought forth to the PIs for further discussion and decision-making.

Research Ethics Approval

Ethics approval for the study has been obtained from the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary.

DISSEMINATION PLAN

Trial results will be disseminated to patients with a summary sheet that will outline the trial findings in lay language. Results will be disseminated to healthcare professionals and researchers via publication in an academic journal and presentation at academic conferences.

DISCUSSION

Fatigue is a common and disabling symptom of end-stage renal disease(1,4–6), that has traditionally been challenging to mitigate due to its complex and nonspecific etiology. Results from patient-reported outcome and engagement studies have highlighted the need to continue to explore new fatigue management interventions for people with ESRD(5,14). Energy management education (EME) is an approach that has been associated with positive fatigue-

related outcomes in other chronic disease populations. For example, in people with MS, RCTs have found that EME reduces patient fatigue and its impact on physical, cognitive and psychosocial functioning, and improves self-efficacy(20–22,38,39). Earlier-phase studies in acquired brain injury(40), cardiac disease(23,24), and post-polio(41) have similarly shown positive effects on fatigue and other related, high-priority outcomes, such as life participation (23,40). Furthermore, single-case studies conducted in a small sample of ESRD patients have generated promising findings regarding the effects of the PEP program on fatigue and life participation in people on chronic dialysis (25), suggesting this approach has potential to fill an important gap in ESRD care. However, studies in ESRD have thus far lacked important design elements, such as blinding, randomization, and sample representativeness, leaving the true potential of the PEP program unclear.

This proposed pilot RCT will provide several pieces of feasibility information to help plan an RCT, that can more conclusively establish the efficacy of the PEP program in people with ESRD. It will provide more accurate preliminary estimates of program effect sizes than are currently available, enabling greater precision in RCT power and sample size calculations. It will also provide estimates of eligibility, recruitment and attrition rates, which will help to ensure that adequate numbers of patients are approached for the RCT. Finally, it will help us to maximize fidelity to the treatment protocol in the RCT by providing information on the effectiveness of the current staff training program, and the potential need to involve rehabilitation specialists in future program research and implementation. These will all be necessary factors to ensure successful future implementation of an RCT.

The proposed pilot RCT has a number of strengths. The program under investigation (the PEP program) has been tailored specifically to meet the needs of the ESRD population: it is designed to facilitate participation in meaningful activities, which is a high priority for ESRD patients, and is delivered in a flexible format to accommodate the dialysis schedule. Patients have also been consulted and provided input at several stages of intervention development and testing. The study protocol was developed using the SPIRIT guidelines for a pilot RCT protocol, increasing the likelihood that important study design elements have been addressed. We have also developed a standardized training and administration protocol for the PEP program, that we anticipate will maximize treatment fidelity and consistency across program administrators. An active control condition to blind patients to their treatment allocation status will further increase the confidence in our study findings, by controlling for the placebo effect.

Our study also has limitations. First, we are excluding non-English speaking patients from the study, which limits its generalizability to non-English-speaking ESRD populations. However, the findings from this study may help to justify developing program materials in alternative languages that are accessible to a wider range of renal patients. We are also excluding patients outside of the in-center hemodialysis population who also experience a high burden of fatigue (eg. predialysis patients, peritoneal dialysis patients, home hemodialysis patients). This study should be viewed as an important first step in establishing the potential for the PEP program, that can lay the groundwork for future research into energy management education in other renal populations. Finally, we are unable to blind treatment administrators to treatment allocation, due to our inability to conceal which study condition is the treatment condition. We perceive blinding to be unfeasible because treatment administrators would be able to identify the treatment

condition, based on inequities between the two conditions in the amount of content dedicated to fatigue and the length of time spent on staff training. The infeasibility of blinding is a well-recognized limitation of trials studying psychosocial or behavioural interventions that are not easily matched with an equivalent control.

In conclusion, the findings from this pilot RCT will further our understanding of a program that has potential to address the challenging problem of fatigue in the ESRD patient population.

TRIAL STATUS

The study started recruitment at the end of February 2019. Recruitment will continue until August 2019. Data collection will conclude in January 2020.

AUTHOR CONTRIBUTIONS

Dr. Janine Farragher and Dr. Brenda Hemmelgarn led the design and writing of the pilot RCT protocol. Dr. Chandra Thomas and Dr. Braden Manns helped with the development of the participant identification plan, and provided advice on other key study issues. Dr. Pietro Ravani and Dr. Meghan Elliott contributed feedback on trial design. All authors contributed important intellectual content to the written protocol and approved the final version for publication.

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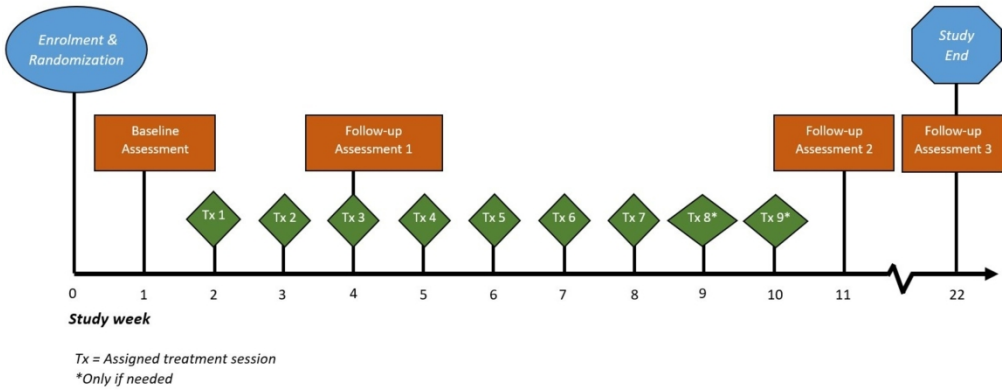
FIGURE LEGENDS

Figure 1: Participant Timeline



Participant Timeline

1276x510mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3

Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	4
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 & 21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	10
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Table 4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Table 4
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A (low-risk trial)
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
6Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	4
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A