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

Protocol v1.0 – March 7, 2019

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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](http://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 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-

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3 friendly meals; attending dialysis or performing home exchanges). However, EME has never  
4  
5 been tested in the ESRD population.  
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8  
9 We developed a personalized, web-supported EME program (the “PEP” Program), tailored for  
10  
11 the ESRD population. The program is designed specifically to reduce the impact of fatigue on  
12  
13 life participation, and is delivered in a flexible, web-supported format to accommodate patients’  
14  
15 demanding dialysis schedules. Preliminary usability and acceptability testing found that the  
16  
17 program was well received, while several single-case studies found that people with ESRD  
18  
19 experienced a small to moderate decrease in fatigue and disability after participating in the  
20  
21 program. These positive preliminary findings justify a randomized controlled trial (RCT) to more  
22  
23 conclusively establish the efficacy of the PEP program.  
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30 However, additional information is first needed to design and plan an RCT. First, we need to  
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32 establish the feasibility of an RCT on the PEP program. Poor recruitment and high attrition rates  
33  
34 are common in clinical trials involving ESRD patients, with high illness burden as one possible  
35  
36 factor. This could be problematic for a study of an educational program like the PEP program,  
37  
38 that will require substantial patient engagement and participation. Second, we need to understand  
39  
40 the feasibility of training non-rehabilitation clinicians (eg. nurses) to administer the PEP program  
41  
42 for future knowledge translation and program planning purposes, as rehabilitation therapists  
43  
44 (who typically administer energy management education programs) are often absent from  
45  
46 dialysis units. Finally, we need to collect more data on the effects of the program on possible  
47  
48 primary outcomes (fatigue and life participation) to determine the optimal primary outcome  
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50 measure for an RCT, estimate the sample size for an RCT, and establish maintenance of short-  
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52 term effects of the PEP program on patient fatigue and life participation.  
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## 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
<ol style="list-style-type: none"> <li>1. Aged <math>\geq 18</math> years</li> <li>2. On chronic dialysis therapy for <math>\geq 3</math> months at time of recruitment</li> <li>3. Clinically and cognitively stable (able to provide informed consent)</li> <li>4. Scores an avg. of <math>\geq 4</math> on items 5, 7, 8 and 9 of the Fatigue Severity Scale</li> </ol>	<ol style="list-style-type: none"> <li>1. Inadequate written and verbal English comprehension for study activities</li> <li>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)</li> <li>3. Resides in a nursing home facility</li> <li>4. Preclusive visual impairment</li> </ol>

### 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

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3 adults with fatigue. Blinding of treatment administrators will not be feasible, given their required  
4  
5 level of familiarity with both the treatment and control conditions.  
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### 8 **Treatment: The “PEP” Program**

9  
10 Participants randomized to the treatment condition will undergo the “PEP” (Personal Energy  
11  
12 Planning) program. The PEP program is an energy management education program that  
13  
14 combines general education about energy management with individualized training to develop  
15  
16 personal energy management strategies. The program is delivered over 7-9 weekly sessions, that  
17  
18 are ~20-30 minutes in duration and administered either in person or via telephone (based on  
19  
20 patient preference). The program will be administered by a trained study clinician (occupational  
21  
22 therapist or nurse). It consists of two parts that are described below.  
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27 Part 1: Participants complete two educational computer modules (20-30 mins each) that explain  
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29 basic principles related to energy management (eg. energy budgeting; prioritizing; seven key  
30  
31 energy-saving strategies), and include activities and exercises to reinforce key concepts. The  
32  
33 modules are publicly accessible online ([www.pepmodule1.com](http://www.pepmodule1.com); [www.pepmodule2.com](http://www.pepmodule2.com)), and  
34  
35 can be completed by patients independently (with support provided to access technology, as  
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37 needed).  
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42 Part 2: Participants learn how to apply the energy management principles from Part 1 to  
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44 accomplish their own life participation goals. First, participants work with a study clinician to  
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46 identify 3 personal life participation goals (eg. to be able to do the grocery shopping weekly).  
47  
48 They then complete a web module ([www.pepmodule3.com](http://www.pepmodule3.com)) that explains a method to identify  
49  
50 *personalized* energy management strategies that will facilitate their goals. The method used is an  
51  
52 adapted version of the Cognitive Orientation to Occupational Performance (CO-OP)  
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54 intervention(14), which is an evidence-based approach to cognitive skill acquisition(15). Key  
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3 elements of CO-OP used are dynamic performance analysis (ie. analyzing where the participant  
4 is expending excessive amounts of energy during each goal activity); goal-plan-do-check (ie.,  
5 generating energy management “plans”, “doing” the plans, and “checking” to see if they work),  
6 and guided discovery (a method of questioning and cueing used by the study clinician to enable  
7 the participant to discover energy management solutions themselves). Participants spend 5-7  
8 program sessions (15-30 mins each) applying the CO-OP approach with the study clinician to  
9 develop and test personalized energy management strategies for accomplishing their goals. The  
10 process is continued until an optimal performance solution is found for each goal; or, the  
11 program maximum of 9 weekly treatment sessions are reached (whichever comes first).  
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13 Participants are also given a program workbook to guide them throughout the PEP program.  
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### 27 **Control: General Information about Kidney Disease**

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

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46 Study coordinators will monitor and encourage participant adherence to the treatment protocol  
47 during weekly visits. All missed or incomplete treatment sessions will be documented.  
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### 51 **Staff Training**

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53 All treatment administrators will undergo training in how to administer the treatment and control  
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3 protocols. A training manual for treatment and control conditions will also be provided. Training  
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5 materials can be obtained by contacting the study corresponding author.  
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### 8 **Concomitant Care**

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

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

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32 Demographic	33 Clinical
34 Age	Dialysis vintage
35 Sex	Comorbidities
36 Residence type	Most recent hemoglobin
37 Living status	Most recent albumin
38 Marital status	ADL independence
39 Employment	Cognitive function
40 Education	(MiniCOG)
	Depression (PHQ-2)

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50 The number of screened patients who meet study inclusion and exclusion criteria; consent to  
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52 participation and randomization; and complete all study procedures will be documented by study  
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3 staff. Follow-up information (including recent hospitalizations, illnesses, dialysis changes,  
4 exercise changes, lab data) will be documented at each follow-up visit.  
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8 The following questionnaires of fatigue and life participation will be administered at four  
9 timepoints (Figure 1), except the COPM, which will not be administered at Baseline. The 4  
10 timepoints are: Baseline (at first study visit); Post-Part 1 of the PEP program (just prior to  
11 commencing Part 2, session 1); Post-Part 2 of the PEP program (one week after the final study  
12 visit); and 12 weeks after the final study visit. Questionnaires will be completed before, during,  
13 or after a dialysis session, according to participant preference. The timing and location of  
14 questionnaire completion will be kept consistent across assessment timepoints for each  
15 participant.  
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### 26 27 28 Fatigue Severity Scale (FSS)

29 The FSS(17) asks individuals to rate, on a Likert scale from one to seven, the severity of their  
30 fatigue and its impact on their life during the past week. The FSS is a valid, reliable and  
31 responsive measure(18,19) that has previously been used in the dialysis population(20).  
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### 37 38 Fatigue Management Questionnaire (FMQ)

39 The FMQ asks participants to rate various aspects of their fatigue management (eg. competence,  
40 satisfaction, self-efficacy) on a Likert Scale of 1-10. The questionnaire was created for this study  
41 to fill a gap in assessments that measure competence and self-efficacy specifically related to  
42 fatigue management.  
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### 48 49 Modified Fatigue Impact Scale (MFIS)

50 The MFIS(21) is a 21-item Likert-based scale that assesses the effects of fatigue on physical,  
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3 cognitive, and psychosocial functioning. The Fatigue Impact Scale has frequently been used as  
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5 an outcome measure in energy management education studies.  
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#### 7 8 Reintegration to Normal Living Index (RNLI)

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10 The RNLI(22) assesses the degree to which individuals who have experienced traumatic or  
11  
12 incapacitating illness achieve reintegration into normal social activities, using 11 declarative  
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14 statements that are accompanied by a visual analogue scale (VAS). The RNLI has been found to  
15  
16 have strong validity and reliability in multiple disease populations(23).  
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#### 19 20 Canadian Occupational Performance Measure (COPM)

21  
22 The COPM(24) is designed to capture a client's self-perception of performance in three specific  
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24 priority tasks of everyday living. It asks individuals to rate, on a 10-point Likert scale, the  
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26 importance of three self-chosen priority activities; their current perceived performance on the  
27  
28 priority activities; and their satisfaction with that performance. The COPM has been found to be  
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30 a valid, reliable, clinically useful and responsive outcome measure in multiple disease  
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32 populations(25).  
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37 All treatment sessions (excluding computer modules) will be audio-recorded on an audio  
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39 recording device, to allow for evaluation of treatment fidelity of the program administrators  
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41 using the CO-OP fidelity checklist. The checklist includes 26 items, each scored on a scale of 0-  
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43 5, that measure the extent of use of various key elements of the treatment approach by the  
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45 treatment administrator.  
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#### 48 49 **Data Management & Confidentiality**

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51 Study data will be recorded onto standardized paper study forms at the time of collection. Data  
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53 will be anonymized by assigning each participant an unidentifiable study ID number at the time  
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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
<ul style="list-style-type: none"> <li>a. Failure to initiate treatment within 2 weeks of study screening &amp; enrolment</li> <li>b. Missed <math>\geq 3</math> consecutive treatment or control sessions, leading to discontinuation of assigned treatment condition (but not withdrawal from study)</li> </ul>



- c. Missed  $\geq 2$  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 <u>1-2</u> 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 <u>3 or more</u> 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 <u>&gt;1 week</u>	-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:

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

### 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  $\leq 20\%$ . 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

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2  
3 consultation and feedback on the first intervention prototype that led to several program  
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5 modifications. Patients were also consulted on the content and format of the control condition to  
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7 be used in this study. Our current study team includes a patient partner who will be consulted  
8  
9 about patient-related issues that arise during the study, the interpretation of results, and strategies  
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11 to optimize dissemination and uptake.  
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## 14 15 **ETHICAL CONSIDERATIONS**

### 16 17 **Risks and Benefits**

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19 As part of their baseline assessment, participants will complete the PHQ-2 depression screening  
20  
21 assessment. This assessment may identify individuals who have, or are at risk for, clinical  
22  
23 depression. Any individual who scores  $>2$  on the PHQ-2 will be offered connection to support  
24  
25 services, such as referral to their clinical social worker, or to a local counselling centre. Study  
26  
27 participants will also have to complete several study questionnaires, and participate in PEP  
28  
29 program treatment sessions. There is a risk that patients may experience short-term fatigue, or,  
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31 uncomfortable or unpleasant emotions in response to some of the questions in the study  
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33 questionnaires. Participants will therefore be advised that they can skip any questions or study  
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35 procedures that make them uncomfortable.  
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43 Direct benefits of participating are those which may be gained from completing the study  
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45 intervention, such as improved fatigue management, improved knowledge about kidney disease,  
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47 and/or and increased staff attention. Indirect benefits include the potential that others with kidney  
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49 disease may benefit from the study findings in the future.  
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### **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

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3 active control condition to blind patients to their treatment allocation status will further increase  
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5 the confidence in our study findings, by controlling for the placebo effect.  
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10 Our study also has limitations. First, we are excluding non-English speaking patients from the  
11 study, which limits its generalizability to non-English-speaking ESRD populations. However, the  
12 findings from this study may help to justify developing program materials in alternative  
13 languages that are accessible to a wider range of renal patients. We are also excluding patients  
14 outside of the in-center hemodialysis population who also experience a high burden of fatigue  
15 (eg. predialysis patients, peritoneal dialysis patients, home hemodialysis patients). This study  
16 should be viewed as an important first step in establishing the potential for the PEP program, that  
17 can lay the groundwork for future research into energy management education in other renal  
18 populations. Finally, we are unable to blind treatment administrators to treatment allocation, due  
19 to our inability to conceal which study condition is the treatment condition. We perceive blinding  
20 to be unfeasible because treatment administrators would be able to identify the treatment  
21 condition, based on inequities between the two conditions in the amount of content dedicated to  
22 fatigue and the length of time spent on staff training. The infeasibility of blinding is a well-  
23 recognized limitation of trials studying psychosocial or behavioural interventions that are not  
24 easily matched with an equivalent control.  
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47 In conclusion, the findings from this pilot RCT will inform the plan for participant accrual for an  
48 RCT of the PEP program, the primary outcome and sample size to be used, and methods to  
49 optimize protocol uptake and fidelity. This research will further our understanding of a program  
50 that has potential to address the challenging problem of fatigue in the ESRD patient population.  
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## 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.

For peer review only



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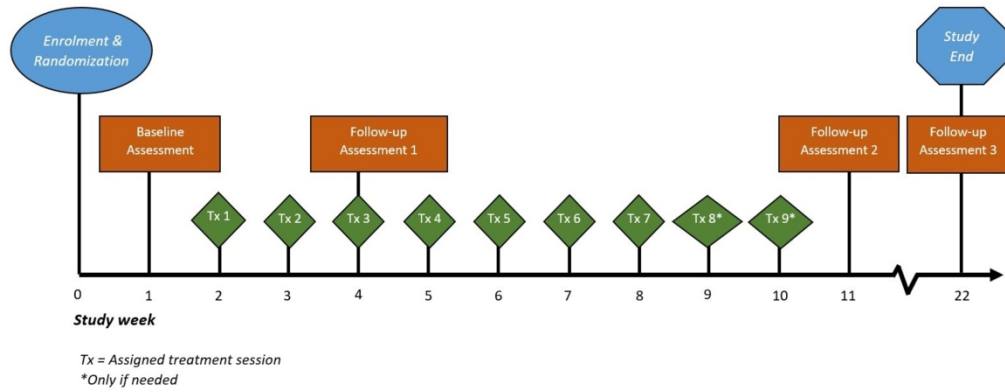
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**FIGURE LEGENDS**

Figure 1: Participant Timeline

For peer review only

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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	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	3

1	Trial registration:	<a href="#">#2b</a>	All items from the World Health Organization Trial	N/A
2				
3	data set		Registration Data Set	
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6	Protocol version	<a href="#">#3</a>	Date and version identifier	1
7				
8				
9	Funding	<a href="#">#4</a>	Sources and types of financial, material, and other	4
10			support	
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14				
15	Roles and	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	1 & 21
16	responsibilities:			
17				
18	contributorship			
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22	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	N/A
23	responsibilities:			
24				
25	sponsor contact			
26				
27	information			
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31	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study	N/A
32	responsibilities:		design; collection, management, analysis, and	
33			interpretation of data; writing of the report; and the	
34	sponsor and funder		decision to submit the report for publication, including	
35			whether they will have ultimate authority over any of	
36			these activities	
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46	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the	N/A
47	responsibilities:		coordinating centre, steering committee, endpoint	
48			adjudication committee, data management team, and	
49	committees		other individuals or groups overseeing the trial, if	
50			applicable (see Item 21a for data monitoring committee)	
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1	Background and	<a href="#">#6a</a>	Description of research question and justification for	5
2				
3	rationale		undertaking the trial, including summary of relevant	
4				
5			studies (published and unpublished) examining benefits	
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7			and harms for each intervention	
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11	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	10
12				
13	rationale: choice of			
14				
15	comparators			
16				
17				
18	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	7
19				
20				
21				
22	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg,	7
23				
24			parallel group, crossover, factorial, single group),	
25				
26			allocation ratio, and framework (eg, superiority,	
27				
28			equivalence, non-inferiority, exploratory)	
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30				
31	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic,	7
32				
33			academic hospital) and list of countries where data will	
34				
35			be collected. Reference to where list of study sites can	
36				
37			be obtained	
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41	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If	Table 1
42				
43			applicable, eligibility criteria for study centres and	
44				
45			individuals who will perform the interventions (eg,	
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47			surgeons, psychotherapists)	
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51	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow	9
52				
53	description		replication, including how and when they will be	
54				
55			administered	
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1	Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated	Table 4
2				
3	modifications		interventions for a given trial participant (eg, drug dose	
4			change in response to harms, participant request, or	
5			improving / worsening disease)	
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11	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention	10
12				
13	adherence		protocols, and any procedures for monitoring adherence	
14			(eg, drug tablet return; laboratory tests)	
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19	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are	11
20			permitted or prohibited during the trial	
21	concomitant care			
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24	Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the	11
25			specific measurement variable (eg, systolic blood	
26			pressure), analysis metric (eg, change from baseline,	
27			final value, time to event), method of aggregation (eg,	
28			median, proportion), and time point for each outcome.	
29			Explanation of the clinical relevance of chosen efficacy	
30			and harm outcomes is strongly recommended	
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41	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any	Figure 1
42			run-ins and washouts), assessments, and visits for	
43			participants. A schematic diagram is highly	
44			recommended (see Figure)	
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51	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve	16
52			study objectives and how it was determined, including	
53			clinical and statistical assumptions supporting any	
54			sample size calculations	
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1	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment	16
2			to reach target sample size	
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6	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg,	8
7	generation		computer-generated random numbers), and list of any	
8			factors for stratification. To reduce predictability of a	
9			random sequence, details of any planned restriction (eg,	
10			blocking) should be provided in a separate document	
11			that is unavailable to those who enrol participants or	
12			assign interventions	
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23	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence	8
24	concealment		(eg, central telephone; sequentially numbered, opaque,	
25			sealed envelopes), describing any steps to conceal the	
26			sequence until interventions are assigned	
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33	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will	8
34	implementation		enrol participants, and who will assign participants to	
35			interventions	
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41	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions	8
42			(eg, trial participants, care providers, outcome	
43			assessors, data analysts), and how	
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48	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	N/A
49	emergency		permissible, and procedure for revealing a participant's	
50			allocated intervention during the trial	
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1	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome,	11
2			baseline, and other trial data, including any related	
3			processes to promote data quality (eg, duplicate	
4			measurements, training of assessors) and a description	
5			of study instruments (eg, questionnaires, laboratory	
6			tests) along with their reliability and validity, if known.	
7				
8			Reference to where data collection forms can be found,	
9			if not in the protocol	
10				
11	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete	Table 4
12	retention		follow-up, including list of any outcome data to be	
13			collected for participants who discontinue or deviate from	
14			intervention protocols	
15				
16	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage,	13
17			including any related processes to promote data quality	
18			(eg, double data entry; range checks for data values).	
19			Reference to where details of data management	
20			procedures can be found, if not in the protocol	
21				
22	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary	15
23			outcomes. Reference to where other details of the	
24			statistical analysis plan can be found, if not in the	
25			protocol	
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27	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and	N/A
28	analyses		adjusted analyses)	
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1	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	16
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3	population and		adherence (eg, as randomised analysis), and any	
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5	missing data		statistical methods to handle missing data (eg, multiple	
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7			imputation)	
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11	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC);	18
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13	formal committee		summary of its role and reporting structure; statement of	
14				
15			whether it is independent from the sponsor and	
16			competing interests; and reference to where further	
17			details about its charter can be found, if not in the	
18			protocol. Alternatively, an explanation of why a DMC is	
19			not needed	
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28	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping	N/A
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30	interim analysis		guidelines, including who will have access to these	
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32			interim results and make the final decision to terminate	
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34			the trial	
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38	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing	N/A (low-
39				risk trial)
40			solicited and spontaneously reported adverse events	
41				
42			and other unintended effects of trial interventions or trial	
43				
44			conduct	
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48	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if	N/A
49				
50			any, and whether the process will be independent from	
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52			investigators and the sponsor	
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55	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee /	18
56				
57	approval		institutional review board (REC / IRB) approval	
58				
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1	Protocol	<a href="#">#25</a>	Plans for communicating important protocol	14
2				
3	amendments		modifications (eg, changes to eligibility criteria,	
4			outcomes, analyses) to relevant parties (eg,	
5			investigators, REC / IRBs, trial participants, trial	
6			registries, journals, regulators)	
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13	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from	7
14			potential trial participants or authorised surrogates, and	
15			how (see Item 32)	
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21	6Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	N/A
22			participant data and biological specimens in ancillary	
23	ancillary studies		studies, if applicable	
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28	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	13
29			participants will be collected, shared, and maintained in	
30			order to protect confidentiality before, during, and after	
31			the trial	
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38	Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	4
39			investigators for the overall trial and each study site	
40	interests			
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44	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial	N/A
45			dataset, and disclosure of contractual agreements that	
46			limit such access for investigators	
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51	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	N/A
52			compensation to those who suffer harm from trial	
53	trial care		participation	
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1	Dissemination	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	18
2				
3	policy: trial results		results to participants, healthcare professionals, the	
4			public, and other relevant groups (eg, via publication,	
5			reporting in results databases, or other data sharing	
6			arrangements), including any publication restrictions	
7				
8	Dissemination	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	N/A
9				
10	policy: authorship		professional writers	
11				
12	Dissemination	<a href="#">#31c</a>	Plans, if any, for granting public access to the full	N/A
13				
14	policy: reproducible		protocol, participant-level dataset, and statistical code	
15				
16	research			
17				
18	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation	Appendix
19				
20	materials		given to participants and authorised surrogates	
21				
22	Biological	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
23				
24	specimens		biological specimens for genetic or molecular analysis in	
25			the current trial and for future use in ancillary studies, if	
26			applicable	
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 42 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-  
 43 BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool made  
 44 by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# 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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<b>Primary Subject Heading</b>:	Renal medicine
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Keywords:	Fatigue, End stage renal failure < NEPHROLOGY, Rehabilitation medicine < INTERNAL MEDICINE, Randomized Controlled Trial

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**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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**Word Count:** 4081



## 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](http://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, Erythropoetin 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

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2  
3 such as insufficient staff expertise and low patient motivation(17). Cognitive-behavioural  
4 therapy for fatigue is an approach targeting unhelpful beliefs and behaviours related to fatigue  
5 that has shown promising results in other populations (18,19), and is currently under  
6 investigation for people with ESRD(11). Energy management education (EME) is yet another  
7 approach to fatigue management, that has also been associated with improvements in other  
8 chronic disease populations, such as multiple sclerosis(20–22) and cardiac disease(23,24). The  
9 theory behind EME is that fatigue in chronic disease is exacerbated when an individual's energy  
10 capacity exceeds their energy expenditure during day-to-day activities, which can consequently  
11 interfere with life participation. The objective of EME is therefore to provide practical strategies  
12 (eg. prioritizing, using efficient body postures, organizing the home environment) to reduce  
13 energy expenditure during everyday life, minimize fatigue and maximize life participation. EME  
14 may be well-suited to meet the needs of people with ESRD, as they have been found to have a  
15 reduced energy capacity compared to healthy populations (6), and must also expend extra energy  
16 on multiple health management tasks associated with dialysis (eg. planning and preparing renal-  
17 friendly meals; attending dialysis or performing home dialysis; monitoring fluid intake and blood  
18 pressure) in addition to usual daily activities. To date, EME has never been studied in the ESRD  
19 population.

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21  
22 We developed a personalized, web-supported EME program (the “PEP” Program), that has been  
23 tailored for the ESRD population in several ways. The program is designed specifically to target  
24 the impact of fatigue on life participation, in accordance with patient-identified priorities, by  
25 using a personalized, goal-focused intervention approach. It is also delivered in a concise,  
26 flexible, and web-supported format, to accommodate patients' time restrictions resulting from  
27 their dialysis schedules. Preliminary acceptability testing found that the program was both

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3 practical and well-received based on feedback from patient interviews(25), while five single-case  
4 studies revealed small to moderate improvements in fatigue and life participation associated with  
5 the program in people with ESRD (according to Tau-U statistic of effect-size estimates and in-  
6 depth patient interviews) (25). These positive preliminary findings justify a randomized  
7 controlled trial (RCT) to more conclusively establish the efficacy of the PEP program.  
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17 However, additional information is first needed to design and plan an RCT. First, we need to  
18 establish the feasibility of an RCT on the PEP program. Poor recruitment and high attrition rates  
19 are common in clinical trials involving ESRD patients, with high illness burden as one possible  
20 factor. This could be problematic for a study of an educational program such as the PEP program  
21 that will require substantial patient engagement and participation. Second, we need to understand  
22 the feasibility of training non-rehabilitation clinicians (eg. nurses) to administer the PEP program  
23 for future knowledge translation and program planning purposes, as rehabilitation therapists  
24 (who typically administer energy management education programs) are often absent from  
25 dialysis units. Finally, we need to collect more data on the effects of the program on possible  
26 primary outcomes (fatigue and life participation) to determine the optimal primary outcome  
27 measure for an RCT, estimate the sample size for a an RCT, and establish longer-term effects of  
28 the PEP program on patient fatigue and life participation.  
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## 45 **OBJECTIVES**

### 46 **Primary Objective**

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49 1. To estimate the proportion of ESRD patients that are eligible for an RCT of the PEP program,  
50 will consent to participate, and will complete all study procedures  
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## 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 $\geq 18$ years	1. Inadequate written and verbal English comprehension for study activities
2. On chronic dialysis therapy for $\geq 3$ months at time of recruitment	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. Clinically and cognitively stable (able to provide informed consent)	3. Resides in a nursing home facility
4. Scores an avg. of $\geq 4$ on items 5, 7, 8 and 9 of the Fatigue Severity Scale	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](http://www.pepmodule1.com); [www.pepmodule2.com](http://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](http://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-

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3 check (ie., generating energy management “plans”, “doing” the plans, and “checking” to see if  
4 they work), and guided discovery (a method of questioning and cueing used by the study  
5 clinician to enable the participant to discover energy management strategies themselves).

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10 Participants spend 5-7 program sessions (15-30 mins each) applying the CO-OP approach with  
11 the study clinician to develop and test personalized energy management strategies for  
12 accomplishing their goals. The process is continued until an optimal performance solution is  
13 found for each goal; or, the program maximum of 9 weekly treatment sessions are reached  
14 (whichever comes first). Participants are also given a program workbook to guide them  
15 throughout the PEP program.  
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### 24 **Control: General Information about Kidney Disease**

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

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43 Study coordinators will monitor and encourage participant adherence to the treatment protocol  
44 during weekly visits. All missed or incomplete treatment sessions will be documented.  
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### 48 **Staff Training**

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

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

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

32 <b>Demographic</b>	33 <b>Clinical</b>
34 Age	35 Dialysis vintage
36 Sex	37 Comorbidities
38 Residence type	39 Most recent hemoglobin
40 Living status	41 Most recent albumin
42 Marital status	43 ADL independence
44 Employment	45 Cognitive function
46 Education	47 (MiniCOG)
	48 Depression (PHQ-2)

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52 The number of screened patients who meet study inclusion and exclusion criteria; consent to  
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54 participation and randomization; and complete all study procedures will be documented by study  
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3 staff. Follow-up information (including recent hospitalizations, illnesses, dialysis changes,  
4 exercise changes, serum hemoglobin and albumin) will be documented at each follow-up visit.  
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7  
8 The following questionnaires will be used to measure fatigue and life participation outcomes.  
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10 These questionnaires were selected based on patient-reported priorities such as minimizing the  
11 burden of administration, limiting the recall period, and capturing the impact of fatigue on life  
12 participation (5).  
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#### 16 17 18 Fatigue Severity Scale (FSS)

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20 The FSS(29) asks individuals to rate, on a Likert scale from one to seven, the severity of their  
21 fatigue and its impact on their life during the past week. The FSS is a valid, reliable and  
22 responsive measure(30,31) that has previously been used in the dialysis population(12).  
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#### 26 27 28 Fatigue Management Questionnaire (FMQ)

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30 The FMQ asks participants to rate various aspects of their fatigue management (eg. competence,  
31 satisfaction, self-efficacy) on a Likert Scale of 1-10. The questionnaire was created for this study  
32 to fill a gap in assessments that measure life participation and self-efficacy specifically related to  
33 fatigue management.  
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#### 40 41 42 Modified Fatigue Impact Scale (MFIS)

43 The MFIS(32) is a 21-item Likert-based scale that assesses the effects of fatigue on physical,  
44 cognitive, and psychosocial functioning. The Fatigue Impact Scale has frequently been used as  
45 an outcome measure in energy management education studies.  
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#### 50 51 52 Reintegration to Normal Living Index (RNLI)

53 The RNLI(33) assesses the degree to which individuals who have experienced traumatic or  
54 incapacitating illness achieve reintegration into normal social activities, using 11 declarative  
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3 statements that are accompanied by a visual analogue scale (VAS). The RNLI has been found to  
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5 have strong validity and reliability in multiple disease populations(34).  
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#### 8 Canadian Occupational Performance Measure (COPM) 9

10 The COPM(35) is designed to capture a client's perception of his/her performance in three  
11  
12 priority tasks of everyday living. It asks individuals to rate, on a 10-point Likert scale, the  
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14 importance of three self-chosen priority activities; their current perceived performance on the  
15  
16 importance of three self-chosen priority activities; their current perceived performance on the  
17  
18 priority activities; and their satisfaction with that performance. The COPM has been found to be  
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20 a valid, reliable, clinically useful and responsive outcome measure in multiple disease  
21  
22 populations(36).  
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25 The fatigue and life participation questionnaires will be administered at four timepoints (Figure  
26  
27 1) (except the COPM, which will not be administered at baseline):  
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29

- 30 1. Pre-intervention baseline
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- 32 2. Post-Part 1 of the PEP program (just prior to commencing Part 2, session 1)
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- 34 3. Post-Part 2 of the PEP program (one week after the final study visit)
- 35
- 36 4. 12 weeks after the final study visit
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40 Questionnaires will be completed before, during, or after a dialysis session, according to  
41  
42 participant preference. The timing and location of questionnaire completion will be kept  
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44 consistent across assessment timepoints for each participant.  
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48 All treatment sessions (excluding computer modules) will be audio-recorded on an audio  
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50 recording device. Two sessions per participant randomized to the treatment condition will then  
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52 be randomly selected and used to evaluate treatment fidelity of the program administrators,  
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54 according to the CO-OP fidelity checklist. The checklist includes 26 items, each scored on a  
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3 scale of 0-5, that measure the extent of use of various key elements of the treatment approach by  
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5 the treatment administrator.  
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### 8 **Data Management & Confidentiality**

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10 Study data will be recorded onto standardized paper study forms at the time of collection. Data  
11  
12 will be anonymized by assigning each participant an unidentifiable study ID number at the time  
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14 of enrolment that will be used to identify them for all study materials. Paper data forms will  
15  
16 immediately be filed and stored in a locked office area, and signed study consent forms will be  
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18 filed and stored separately from data forms to maintain participant anonymity.  
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23 Study data will subsequently be entered into a secure database by a research assistant. The  
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25 database will be password protected and stored on a secure server, with access restricted to  
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27 authorized users of the server. Range checks for data values will be performed after data entry, to  
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29 promote data quality.  
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32 Audio recordings of study sessions will also be transferred onto a secure server, and deleted from  
33  
34 their original recording device at the time of transfer. A sample of the audio recordings will  
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36 subsequently be transcribed into text by the team transcriptionist and stored on the secure server.  
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39 Data files and documents will be destroyed 7 years after the project is closed.  
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### 42 **Protocol Deviations and Amendments**

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

Protocol Deviations
<ul style="list-style-type: none"> <li>a. Failure to initiate treatment within 2 weeks of study screening &amp; enrolment</li> <li>b. Missed <math>\geq 3</math> consecutive treatment or control sessions, leading to discontinuation of assigned treatment condition (but not withdrawal from study)</li> <li>c. Missed <math>\geq 2</math> consecutive study assessment visits, leading to non-completion of an assessment package (but not withdrawal from study)</li> <li>d. Participants switch ESRD treatment modality during the course of the study</li> <li>e. Participants are hospitalized overnight during the course of the study</li> <li>f. Dropouts and their causes (eg. withdrawal of consent* or transfer to another centre)</li> </ul>

**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 <u>1-2</u> consecutive weekly treatment sessions	-Missed appointment(s) will be documented

	<ul style="list-style-type: none"> <li>-The scheduled treatment session will be delayed until the next weekly session</li> <li>-Dates of remaining assessment and treatment sessions will be delayed accordingly</li> </ul>
Participant misses <b><u>3 or more</u></b> consecutive weekly treatment sessions	<ul style="list-style-type: none"> <li>-Missed appointments will be documented</li> <li>-Treatment protocol will be discontinued</li> <li>-Treatment discontinuation will be recorded as a Protocol Deviation</li> <li>-Assessment schedule will carry on as planned, regardless of missed treatment sessions</li> </ul>
Participant misses scheduled assessment appointment date and does not complete it during the week of the scheduled date, but completes it the following week	<ul style="list-style-type: none"> <li>-Missed appointment date will be documented</li> <li>-The scheduled assessment will be delayed to the following week</li> <li>-Dates of remaining treatment and assessment sessions will be delayed accordingly</li> </ul>
Participant misses scheduled assessment appointment by <b><u>&gt;1 week</u></b>	<ul style="list-style-type: none"> <li>-Missed appointment will be documented</li> <li>-Missed assessment will be recorded as a Protocol Deviation</li> <li>-No additional attempts will be made to complete the missed assessment</li> </ul>

## 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.



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3 The proportion of patients meeting each of the feasibility endpoints (eligibility, recruitment and  
4 attrition rates), with accompanying 95% confidence intervals, will be calculated.  
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8 Assuming a normal distribution, standardized effect sizes for each fatigue & disability outcome  
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10 measure will be calculated for both immediate post-intervention and three months post-  
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12 intervention, as follows:  
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$$14 \quad \text{Cohen's D} = \frac{\text{Mean pre-post change (treatment)} - \text{Mean pre-post change (control)}}{\text{Standard deviation (pooled)}} \\ 15 \\ 16 \\ 17 \\ 18 \\ 19 \\ 20 \\ 21$$

22 These data will be analyzed using intention-to treat analysis. Sample size calculations for the  
23  
24 RCT will be made using the treatment effect size and variance estimates from the immediate  
25  
26 post-intervention change data for the selected outcome measure. Missing follow-up data will be  
27  
28 addressed using pairwise deletion.  
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31  
32 The treatment fidelity of treatment administrators will be analyzed by calculating an average  
33  
34 score out of 5 on the CO-OP fidelity checklist, for one treatment session per participant  
35  
36 randomized to the treatment condition.  
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### 39 40 **SAMPLE SIZE AND FEASIBILITY** 41

42  
43 A sample size of 40 patients (20 per treatment arm) was chosen to provide a sufficiently precise  
44  
45 estimate of the treatment effect for RCT sample size calculations(37), given 80% power, a small-  
46  
47 medium effect size on fatigue/life participation, and an anticipated attrition rate of  $\leq 20\%$ . There  
48  
49 are approximately 425 prevalent patients on hemodialysis in total at the four participating  
50  
51 clinical sites. Based on conservative estimates of 40% eligibility and 30% recruitment rates, the  
52  
53 patient pool will be adequate to achieve the target sample size for the pilot RCT.  
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## 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

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3 questionnaires. Participants will therefore be advised that they can skip any questions or study  
4  
5 procedures that make them uncomfortable.  
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9 Direct benefits of participating are those which may be gained from completing the study  
10  
11 intervention, such as improved fatigue management, improved knowledge about kidney disease,  
12  
13 and/or and increased staff attention. Indirect benefits include the potential that others with kidney  
14  
15 disease may benefit from the study findings in the future.  
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### 18 19 **Data Safety and Monitoring Board (DSMB)**

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21 As the proposed study is small and its risks to participants are low, a DSMB is not needed.  
22  
23 Monitoring for potential risks (eg. fatigue, discomfort) will be performed by those interacting  
24  
25 directly with the patient during the study (the study clinicians and assessor). If any unexpected  
26  
27 concerns arise that cannot be immediately mitigated, the concerns will be brought forth to the PIs  
28  
29 for further discussion and decision-making.  
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### 33 34 **Research Ethics Approval**

35  
36 Ethics approval for the study has been obtained from the Conjoint Health Research Ethics Board  
37  
38 (CHREB) at the University of Calgary.  
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### 41 42 **DISSEMINATION PLAN**

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44  
45 Trial results will be disseminated to patients with a summary sheet that will outline the trial  
46  
47 findings in lay language. Results will be disseminated to healthcare professionals and researchers  
48  
49 via publication in an academic journal and presentation at academic conferences.  
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### 52 53 **DISCUSSION**

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2  
3 Fatigue is a common and disabling symptom of end-stage renal disease(1,4–6), that has  
4  
5 traditionally been challenging to mitigate due to its complex and nonspecific etiology. Results  
6  
7 from patient-reported outcome and engagement studies have highlighted the need to continue to  
8  
9 explore new fatigue management interventions for people with ESRD(5,14). Energy  
10  
11 management education (EME) is an approach that has been associated with positive fatigue-  
12  
13 related outcomes in other chronic disease populations. For example, in people with MS, RCTs  
14  
15 have found that EME reduces patient fatigue and its impact on physical, cognitive and  
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17 psychosocial functioning, and improves self-efficacy(20–22,38,39). Earlier-phase studies in  
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19 acquired brain injury(40), cardiac disease(23,24), and post-polio(41) have similarly shown  
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21 positive effects on fatigue and other related, high-priority outcomes, such as life participation  
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23 (23,40). Furthermore, single-case studies conducted in a small sample of ESRD patients have  
24  
25 generated promising findings regarding the effects of the PEP program on fatigue and life  
26  
27 participation in people on chronic dialysis (25), suggesting this approach has potential to fill an  
28  
29 important gap in ESRD care. However, studies in ESRD have thus far lacked important design  
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31 elements, such as blinding, randomization, and sample representativeness, leaving the true  
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33 potential of the PEP program unclear.  
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42 This proposed pilot RCT will provide several pieces of feasibility information to help plan an  
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44 RCT, that can more conclusively establish the efficacy of the PEP program in people with  
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46 ESRD. It will provide more accurate preliminary estimates of program effect sizes than are  
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48 currently available, enabling greater precision in RCT power and sample size calculations. It will  
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50 also provide estimates of eligibility, recruitment and attrition rates, which will help to ensure that  
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52 adequate numbers of patients are approached for the RCT. Finally, it will help us to maximize  
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3 fidelity to the treatment protocol in the RCT by providing information on the effectiveness of the  
4 current staff training program, and the potential need to involve rehabilitation specialists in  
5 future program research and implementation. These will all be necessary factors to ensure  
6 successful future implementation of an RCT.  
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14 The proposed pilot RCT has a number of strengths. The program under investigation (the PEP  
15 program) has been tailored specifically to meet the needs of the ESRD population: it is designed  
16 to facilitate participation in meaningful activities, which is a high priority for ESRD patients, and  
17 is delivered in a flexible format to accommodate the dialysis schedule. Patients have also been  
18 consulted and provided input at several stages of intervention development and testing. The  
19 study protocol was developed using the SPIRIT guidelines for a pilot RCT protocol, increasing  
20 the likelihood that important study design elements have been addressed. We have also  
21 developed a standardized training and administration protocol for the PEP program, that we  
22 anticipate will maximize treatment fidelity and consistency across program administrators. An  
23 active control condition to blind patients to their treatment allocation status will further increase  
24 the confidence in our study findings, by controlling for the placebo effect.  
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42 Our study also has limitations. First, we are excluding non-English speaking patients from the  
43 study, which limits its generalizability to non-English-speaking ESRD populations. However, the  
44 findings from this study may help to justify developing program materials in alternative  
45 languages that are accessible to a wider range of renal patients. We are also excluding patients  
46 outside of the in-center hemodialysis population who also experience a high burden of fatigue  
47 (eg. predialysis patients, peritoneal dialysis patients, home hemodialysis patients). This study  
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3 should be viewed as an important first step in establishing the potential for the PEP program, that  
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5 can lay the groundwork for future research into energy management education in other renal  
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7 populations. Finally, we are unable to blind treatment administrators to treatment allocation, due  
8  
9 to our inability to conceal which study condition is the treatment condition. We perceive blinding  
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11 to be unfeasible because treatment administrators would be able to identify the treatment  
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13 condition, based on inequities between the two conditions in the amount of content dedicated to  
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15 fatigue and the length of time spent on staff training. The infeasibility of blinding is a well-  
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17 recognized limitation of trials studying psychosocial or behavioural interventions that are not  
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19 easily matched with an equivalent control.  
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26 In conclusion, the findings from this pilot RCT will further our understanding of a program that  
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28 has potential to address the challenging problem of fatigue in the ESRD patient population.  
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### 32 33 **TRIAL STATUS**

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35 The study started recruitment at the end of February 2019. Recruitment will continue until  
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37 August 2019. Data collection will conclude in January 2020.  
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### 41 **AUTHOR CONTRIBUTIONS**

42  
43  
44 Dr. Janine Farragher and Dr. Brenda Hemmelgarn led the design and writing of the pilot RCT  
45  
46 protocol. Dr. Chandra Thomas and Dr. Braden Manns helped with the development of the  
47  
48 participant identification plan, and provided advice on other key study issues. Dr. Pietro Ravani  
49  
50 and Dr. Meghan Elliott contributed feedback on trial design.  
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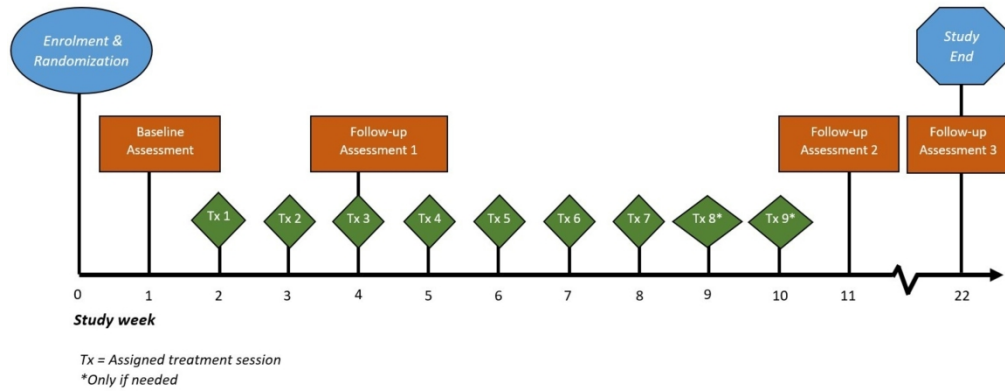
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3 **FIGURE LEGENDS**  
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6 Figure 1: Participant Timeline  
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For peer review only

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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	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	3

1	Trial registration:	<a href="#">#2b</a>	All items from the World Health Organization Trial	N/A
2				
3	data set		Registration Data Set	
4				
5				
6	Protocol version	<a href="#">#3</a>	Date and version identifier	1
7				
8				
9	Funding	<a href="#">#4</a>	Sources and types of financial, material, and other	4
10			support	
11				
12				
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14				
15	Roles and	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	1 & 21
16	responsibilities:			
17				
18	contributorship			
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23	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	N/A
24	responsibilities:			
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26	sponsor contact			
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28	information			
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32	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study	N/A
33	responsibilities:		design; collection, management, analysis, and	
34			interpretation of data; writing of the report; and the	
35	sponsor and funder		decision to submit the report for publication, including	
36			whether they will have ultimate authority over any of	
37			these activities	
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47	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the	N/A
48	responsibilities:		coordinating centre, steering committee, endpoint	
49			adjudication committee, data management team, and	
50	committees		other individuals or groups overseeing the trial, if	
51			applicable (see Item 21a for data monitoring committee)	
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1	Background and	<a href="#">#6a</a>	Description of research question and justification for	5
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3	rationale		undertaking the trial, including summary of relevant	
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5			studies (published and unpublished) examining benefits	
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7			and harms for each intervention	
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11	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	10
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13	rationale: choice of			
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15	comparators			
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18	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	7
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21				
22	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg,	7
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24			parallel group, crossover, factorial, single group),	
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26			allocation ratio, and framework (eg, superiority,	
27				
28			equivalence, non-inferiority, exploratory)	
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31	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic,	7
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33			academic hospital) and list of countries where data will	
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35			be collected. Reference to where list of study sites can	
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37			be obtained	
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41	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If	Table 1
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43			applicable, eligibility criteria for study centres and	
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45			individuals who will perform the interventions (eg,	
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47			surgeons, psychotherapists)	
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51	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow	9
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53	description		replication, including how and when they will be	
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55			administered	
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1	Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated	Table 4
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3	modifications		interventions for a given trial participant (eg, drug dose	
4			change in response to harms, participant request, or	
5			improving / worsening disease)	
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11	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention	10
12				
13	adherence		protocols, and any procedures for monitoring adherence	
14			(eg, drug tablet return; laboratory tests)	
15				
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19	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are	11
20			permitted or prohibited during the trial	
21	concomitant care			
22				
23				
24	Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the	11
25			specific measurement variable (eg, systolic blood	
26			pressure), analysis metric (eg, change from baseline,	
27			final value, time to event), method of aggregation (eg,	
28			median, proportion), and time point for each outcome.	
29			Explanation of the clinical relevance of chosen efficacy	
30			and harm outcomes is strongly recommended	
31				
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40				
41	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any	Figure 1
42			run-ins and washouts), assessments, and visits for	
43			participants. A schematic diagram is highly	
44			recommended (see Figure)	
45				
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50				
51	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve	16
52			study objectives and how it was determined, including	
53			clinical and statistical assumptions supporting any	
54			sample size calculations	
55				
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1	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment	16
2			to reach target sample size	
3				
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5				
6	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg,	8
7	generation		computer-generated random numbers), and list of any	
8			factors for stratification. To reduce predictability of a	
9			random sequence, details of any planned restriction (eg,	
10			blocking) should be provided in a separate document	
11			that is unavailable to those who enrol participants or	
12			assign interventions	
13				
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23	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence	8
24	concealment		(eg, central telephone; sequentially numbered, opaque,	
25			sealed envelopes), describing any steps to conceal the	
26	mechanism		sequence until interventions are assigned	
27				
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32				
33	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will	8
34	implementation		enrol participants, and who will assign participants to	
35			interventions	
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38				
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41	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions	8
42			(eg, trial participants, care providers, outcome	
43			assessors, data analysts), and how	
44				
45				
46				
47				
48	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	N/A
49	emergency		permissible, and procedure for revealing a participant's	
50			allocated intervention during the trial	
51	unblinding			
52				
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1	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome,	11
2			baseline, and other trial data, including any related	
3			processes to promote data quality (eg, duplicate	
4			measurements, training of assessors) and a description	
5			of study instruments (eg, questionnaires, laboratory	
6			tests) along with their reliability and validity, if known.	
7				
8			Reference to where data collection forms can be found,	
9			if not in the protocol	
10				
11	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete	Table 4
12	retention		follow-up, including list of any outcome data to be	
13			collected for participants who discontinue or deviate from	
14			intervention protocols	
15				
16	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage,	13
17			including any related processes to promote data quality	
18			(eg, double data entry; range checks for data values).	
19			Reference to where details of data management	
20			procedures can be found, if not in the protocol	
21				
22	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary	15
23			outcomes. Reference to where other details of the	
24			statistical analysis plan can be found, if not in the	
25			protocol	
26				
27	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and	N/A
28	analyses		adjusted analyses)	
29				
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1	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	16
2				
3	population and		adherence (eg, as randomised analysis), and any	
4				
5	missing data		statistical methods to handle missing data (eg, multiple	
6				
7			imputation)	
8				
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10				
11	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC);	18
12				
13	formal committee		summary of its role and reporting structure; statement of	
14				
15			whether it is independent from the sponsor and	
16			competing interests; and reference to where further	
17			details about its charter can be found, if not in the	
18			protocol. Alternatively, an explanation of why a DMC is	
19			not needed	
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28	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping	N/A
29				
30	interim analysis		guidelines, including who will have access to these	
31				
32			interim results and make the final decision to terminate	
33				
34			the trial	
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38	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing	N/A (low-
39				risk trial)
40			solicited and spontaneously reported adverse events	
41				
42			and other unintended effects of trial interventions or trial	
43				
44			conduct	
45				
46				
47				
48	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if	N/A
49				
50			any, and whether the process will be independent from	
51				
52			investigators and the sponsor	
53				
54				
55	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee /	18
56				
57	approval		institutional review board (REC / IRB) approval	
58				
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1	Protocol	<a href="#">#25</a>	Plans for communicating important protocol	14
2				
3	amendments		modifications (eg, changes to eligibility criteria,	
4			outcomes, analyses) to relevant parties (eg,	
5			investigators, REC / IRBs, trial participants, trial	
6			registries, journals, regulators)	
7				
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13	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from	7
14			potential trial participants or authorised surrogates, and	
15			how (see Item 32)	
16				
17				
18				
19				
20				
21	6Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	N/A
22			participant data and biological specimens in ancillary	
23	ancillary studies		studies, if applicable	
24				
25				
26				
27				
28	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	13
29			participants will be collected, shared, and maintained in	
30			order to protect confidentiality before, during, and after	
31			the trial	
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38	Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	4
39			investigators for the overall trial and each study site	
40	interests			
41				
42				
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44	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial	N/A
45			dataset, and disclosure of contractual agreements that	
46			limit such access for investigators	
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51	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	N/A
52			compensation to those who suffer harm from trial	
53	trial care		participation	
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1	Dissemination	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	18
2				
3	policy: trial results		results to participants, healthcare professionals, the	
4			public, and other relevant groups (eg, via publication,	
5			reporting in results databases, or other data sharing	
6			arrangements), including any publication restrictions	
7				
8	Dissemination	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	N/A
9				
10	policy: authorship		professional writers	
11				
12	Dissemination	<a href="#">#31c</a>	Plans, if any, for granting public access to the full	N/A
13				
14	policy: reproducible		protocol, participant-level dataset, and statistical code	
15				
16	research			
17				
18	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation	Appendix
19				
20	materials		given to participants and authorised surrogates	
21				
22	Biological	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
23				
24	specimens		biological specimens for genetic or molecular analysis in	
25			the current trial and for future use in ancillary studies, if	
26			applicable	
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43 BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool made  
44 by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# 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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<b>Primary Subject Heading</b>:	Renal medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Fatigue, End stage renal failure < NEPHROLOGY, Rehabilitation medicine < INTERNAL MEDICINE, Randomized Controlled Trial

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**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](http://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

This research is funded through the Interdisciplinary Chronic Disease Collaboration and the Roy and Vi Baay Chair in Kidney Research.

## 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.

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3 The most well-researched approaches for managing fatigue in ESRD are Erythropoetin therapy  
4 to target anemia(15) and exercise training to increase physical fitness (16). These approaches,  
5 while efficacious for some patients, also have limitations. For example, Erythropoetin therapy  
6 does not address the multiple fatigue mechanisms in ESRD beyond anemia, while exercise  
7 training has been challenging to implement and sustain in ESRD clinical practice, due to factors  
8 such as insufficient staff expertise and low patient motivation(17). Cognitive-behavioural  
9 therapy for fatigue is an approach targeting unhelpful beliefs and behaviours related to fatigue  
10 that has shown promising results in other populations (18,19), and is currently under  
11 investigation for people with ESRD(11). Energy management education (EME) is yet another  
12 approach to fatigue management, that has also been associated with improvements in other  
13 chronic disease populations, such as multiple sclerosis(20–22) and cardiac disease(23,24). The  
14 theory behind EME is that fatigue in chronic disease is exacerbated when an individual's energy  
15 capacity exceeds their energy expenditure during day-to-day activities, which can consequently  
16 interfere with life participation. The objective of EME is therefore to provide practical strategies  
17 (eg. prioritizing, using efficient body postures, organizing the home environment) to reduce  
18 energy expenditure during everyday life, minimize fatigue and maximize life participation. EME  
19 may be well-suited to meet the needs of people with ESRD, as they have been found to have a  
20 reduced energy capacity compared to healthy populations (6), and must also expend extra energy  
21 on multiple health management tasks associated with dialysis (eg. planning and preparing renal-  
22 friendly meals; attending dialysis or performing home dialysis; monitoring fluid intake and blood  
23 pressure) in addition to usual daily activities. To date, EME has never been studied in the ESRD  
24 population.  
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3 We developed a personalized, web-supported EME program (the “PEP” Program), that has been  
4 tailored for the ESRD population in several ways. The program is designed specifically to target  
5 the impact of fatigue on life participation, in accordance with patient-identified priorities, by  
6 using a personalized, goal-focused intervention approach. It is also delivered in a concise,  
7 flexible, and web-supported format with minimal homework, to accommodate patients’ time  
8 restrictions resulting from their dialysis schedules. Preliminary acceptability testing found that  
9 the program was both practical and well-received based on feedback from patient interviews(25),  
10 while five single-case studies revealed small to moderate improvements in fatigue and life  
11 participation associated with the program in people with ESRD (according to Tau-U statistic of  
12 effect-size estimates and in-depth patient interviews) (25). These positive preliminary findings  
13 justify a randomized controlled trial (RCT) to more conclusively establish the efficacy of the  
14 PEP program.

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16  
17 However, additional information is first needed to design and plan an RCT. First, we need to  
18 establish the feasibility of an RCT on the PEP program. Poor recruitment and high attrition rates  
19 are common in clinical trials involving ESRD patients, with high illness burden as one possible  
20 factor. This could be problematic for a study of an educational program such as the PEP program  
21 that will require substantial patient engagement and participation. Second, we need to understand  
22 the feasibility of training non-rehabilitation clinicians (eg. nurses) to administer the PEP program  
23 for future knowledge translation and program planning purposes, as rehabilitation therapists  
24 (who typically administer energy management education programs) are often absent from  
25 dialysis units. Finally, we need to collect more data on the effects of the program on possible  
26 primary outcomes (fatigue and life participation) to determine the optimal primary outcome

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3 measure for an RCT, estimate the sample size for a an RCT, and establish longer-term effects of  
4 the PEP program on patient fatigue and life participation.  
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## 8 9 **OBJECTIVES**

### 10 11 **Primary Objective**

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16 1. To estimate the proportion of ESRD patients that are eligible for an RCT of the PEP program,  
17 will consent to participate, and will complete all study procedures  
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### 21 **Secondary Objectives**

22  
23 1. To identify the fatigue or life participation outcome measure that is most sensitive to change  
24 related to the intervention, and estimate the treatment effect size and variability for RCT sample  
25 size calculations  
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29  
30 2. To explore the in the effects of the PEP program on fatigue and life participation at 3 months  
31 post-treatment  
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35 3. To examine treatment fidelity to the PEP program among non-rehabilitation clinical staff after  
36 participating in a short program training course  
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## 41 **METHODS**

### 42 43 **Trial design**

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45  
46 Parallel group, 1:1, pilot randomized controlled trial.  
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### 50 **Participant Identification**

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52 Participants will be recruited from four in-center hemodialysis units in Calgary, Alberta, Canada.  
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54 Patients who would be potentially eligible and interested in the study will be identified by  
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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 $\geq 18$ years	1. Inadequate written and verbal English comprehension for study activities
2. On chronic dialysis therapy for $\geq 3$ months at time of recruitment	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. Clinically and cognitively stable (able to provide informed consent)	3. Resides in a nursing home facility
4. Scores an avg. of $\geq 4$ on items 5, 7, 8 and 9 of the Fatigue Severity Scale	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

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2  
3 study (intervention or active control). All patient study materials and communications will be left  
4  
5 vague, describing the study purpose as being an investigation of an “educational program” for  
6  
7 adults with fatigue. Blinding of treatment administrators will not be feasible, given their required  
8  
9 level of familiarity with both the treatment and control conditions.  
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11

### 12 13 **Treatment: The “PEP” Program**

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15 Participants randomized to the treatment condition will undergo the “PEP” (Personal Energy  
16  
17 Planning) program. The PEP program is a two-part energy management education program, that  
18  
19 provides general education about energy management and individualized training to develop  
20  
21 personalized energy management strategies. The program is delivered over 7-9 weekly sessions,  
22  
23 dependent upon individual patient needs and rates of progress. Sessions are ~20-30 minutes in  
24  
25 duration each, and administered either in person or via telephone (based on patient preference).  
26  
27 The program is administered by a trained study clinician (occupational therapist or nurse).  
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32 Part 1: Participants complete two educational computer modules (20-30 mins each) that explain  
33  
34 basic principles related to energy management (eg. energy budgeting; prioritizing; seven key  
35  
36 energy-saving strategies), and include activities and exercises to reinforce key concepts. The  
37  
38 modules are publicly accessible online ([www.pepmodule1.com](http://www.pepmodule1.com); [www.pepmodule2.com](http://www.pepmodule2.com)), and  
39  
40 can be completed by patients independently (with support provided to access technology, as  
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42 needed).  
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46 Part 2: Participants learn how to apply the energy management principles from Part 1 to  
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48 accomplish their own life participation goals. First, participants work with a study clinician to  
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50 identify 3 personal life participation goals (eg. to be able to do the grocery shopping weekly).  
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52 They then complete a web module ([www.pepmodule3.com](http://www.pepmodule3.com)) that explains a method to identify  
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54 *personalized* energy management strategies that will facilitate their goals. The method is an  
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3 adapted version of the Cognitive Orientation to Occupational Performance (CO-OP)  
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5 intervention(26), which is an evidence-based approach to problem-solving and skill acquisition  
6  
7 (27). Key elements of CO-OP include dynamic performance analysis (ie. analyzing where the  
8  
9 participant is expending excessive amounts of energy during each goal activity); goal-plan-do-  
10  
11 check (ie., generating energy management “plans”, “doing” the plans, and “checking” to see if  
12  
13 they work), and guided discovery (a method of questioning and cueing used by the study  
14  
15 clinician to enable the participant to discover energy management strategies themselves).  
16  
17 Participants spend 5-7 program sessions (15-30 mins each) applying the CO-OP approach with  
18  
19 the study clinician to develop and test personalized energy management strategies for  
20  
21 accomplishing their goals. The process is continued until an optimal performance solution is  
22  
23 found for each goal; or, the program maximum of 9 weekly treatment sessions are reached  
24  
25 (whichever comes first). Participants are also given a program workbook to guide them  
26  
27 throughout the PEP program.  
28  
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32

### 33 **Control: General Information about Kidney Disease**

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35  
36 Participants randomized to the control condition will review information from the Kidney School  
37  
38 learning modules (28), during 6-8 individual sessions with a trained study clinician (occupational  
39  
40 therapist or nurse). The modules contain general information about managing kidney disease,  
41  
42 addressing topics such as diet and heart health. Sessions will take place either in person or via  
43  
44 telephone (based on patient preference). Use of this active control condition will minimize the  
45  
46 risk of bias associated with patients receiving extra staff attention during the treatment condition.  
47  
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### 50 **Treatment Adherence**

51  
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53 Study coordinators will monitor and encourage participant adherence to the treatment protocol  
54  
55 during weekly visits. All missed or incomplete treatment sessions will be documented.  
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### 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)

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2  
3 The number of screened patients who meet study inclusion and exclusion criteria; consent to  
4 participation and randomization; and complete all study procedures will be documented by study  
5 staff. Follow-up information (including recent hospitalizations, illnesses, dialysis changes,  
6 exercise changes, serum hemoglobin and albumin) will be documented at each follow-up visit.  
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11  
12 The following questionnaires will be used to measure fatigue and life participation outcomes.

13  
14 These questionnaires were selected based on patient-reported priorities such as minimizing the  
15 burden of administration, limiting the recall period, and capturing the impact of fatigue on life  
16 participation (5).  
17  
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19

#### 20 21 22 23 Fatigue Severity Scale (FSS)

24  
25 The FSS(29) asks individuals to rate, on a Likert scale from one to seven, the severity of their  
26 fatigue and its impact on their life during the past week. The FSS is a valid, reliable and  
27 responsive measure(30,31) that has previously been used in the dialysis population(12).  
28  
29  
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#### 31 32 33 Fatigue Management Questionnaire (FMQ)

34  
35 The FMQ asks participants to rate various aspects of their fatigue management (eg. competence,  
36 satisfaction, self-efficacy) on a Likert Scale of 1-10. The questionnaire was created for this study  
37 to fill a gap in assessments that measure life participation and self-efficacy specifically related to  
38 fatigue management.  
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#### 43 44 45 Modified Fatigue Impact Scale (MFIS)

46  
47 The MFIS(32) is a 21-item Likert-based scale that assesses the effects of fatigue on physical,  
48 cognitive, and psychosocial functioning. The Fatigue Impact Scale has frequently been used as  
49 an outcome measure in energy management education studies.  
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### 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.

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3 All treatment sessions (excluding computer modules) will be audio-recorded on an audio  
4 recording device. Two sessions per participant randomized to the treatment condition will then  
5  
6 be randomly selected and used to evaluate treatment fidelity of the program administrators,  
7  
8 according to the CO-OP fidelity checklist. The checklist includes 26 items, each scored on a  
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10 scale of 0-5, that measure the extent of use of various key elements of the treatment approach by  
11  
12 the treatment administrator.  
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### 16 17 **Data Management & Confidentiality**

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19 Study data will be recorded onto standardized paper study forms at the time of collection. Data  
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21 will be anonymized by assigning each participant an unidentifiable study ID number at the time  
22  
23 of enrolment that will be used to identify them for all study materials. Paper data forms will  
24  
25 immediately be filed and stored in a locked office area, and signed study consent forms will be  
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27 filed and stored separately from data forms to maintain participant anonymity.  
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31  
32 Study data will subsequently be entered into a secure database by a research assistant. The  
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34 database will be password protected and stored on a secure server, with access restricted to  
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36 authorized users of the server. Range checks for data values will be performed after data entry, to  
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38 promote data quality.  
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42 Audio recordings of study sessions will also be transferred onto a secure server, and deleted from  
43  
44 their original recording device at the time of transfer. A sample of the audio recordings will  
45  
46 subsequently be transcribed into text by the team transcriptionist and stored on the secure server.  
47

48  
49 Data files and documents will be destroyed 7 years after the project is closed.  
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### 51 52 **Protocol Deviations and Amendments**

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54 Protocol deviations are reported in Table 3. Any mid-study protocol modifications will be  
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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
<ul style="list-style-type: none"> <li>a. Failure to initiate treatment within 2 weeks of study screening &amp; enrolment</li> <li>b. Missed <math>\geq 3</math> consecutive treatment or control sessions, leading to discontinuation of assigned treatment condition (but not withdrawal from study)</li> <li>c. Missed <math>\geq 2</math> consecutive study assessment visits, leading to non-completion of an assessment package (but not withdrawal from study)</li> <li>d. Participants switch ESRD treatment modality during the course of the study</li> <li>e. Participants are hospitalized overnight during the course of the study</li> <li>f. Dropouts and their causes (eg. withdrawal of consent* or transfer to another centre)</li> </ul>

### 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 <u>1-2</u> consecutive weekly treatment sessions	<ul style="list-style-type: none"> <li>-Missed appointment(s) will be documented</li> <li>-The scheduled treatment session will be delayed until the next weekly session</li> <li>-Dates of remaining assessment and treatment sessions will be delayed accordingly</li> </ul>
Participant misses <u>3 or more</u> consecutive weekly treatment sessions	<ul style="list-style-type: none"> <li>-Missed appointments will be documented</li> <li>-Treatment protocol will be discontinued</li> <li>-Treatment discontinuation will be recorded as a Protocol Deviation</li> </ul>

	-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 <b>&gt;1 week</b>	-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

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3 post-intervention change data for the selected outcome measure. Missing follow-up data will be  
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5 addressed using pairwise deletion.  
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8 The treatment fidelity of treatment administrators will be analyzed by calculating an average  
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10 score out of 5 on the CO-OP fidelity checklist, for one treatment session per participant  
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12 randomized to the treatment condition.  
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## 16 **SAMPLE SIZE AND FEASIBILITY**

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19 A sample size of 40 patients (20 per treatment arm) was chosen based on the recommendations  
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21 of Whitehead et al. (37). They suggest this sample size will provide a sufficiently precise  
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23 estimate of the treatment effect to minimize the sample needed for a future RCT, assuming 80%  
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25 power, a small-medium effect size (which is expected based on our preliminary data (25)), and  
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27 an attrition rate of no more than  $\leq 25\%$ .  
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32 There are approximately 425 prevalent patients on hemodialysis in total at the four participating  
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34 clinical sites. We project that approximately half (212 patients) will be identified as potential  
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36 participants with fatigue, based on preliminary symptom screening data from the sites. Given  
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38 that this is a high-priority research area among dialysis patients, we conservatively estimate that  
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40 at least 25% (56 patients) of patients with fatigue will agree to participate. Furthermore, we  
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42 expect no more than 25% of patients will subsequently be excluded during eligibility screening.  
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45 This will enable us to achieve the target sample size of 40 patients.  
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## 49 **PATIENT AND PUBLIC INVOLVEMENT**

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52 Patients have been involved, both directly and indirectly, in multiple aspects of this research  
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54 project. The intervention under study was developed in response to results of patient engagement  
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3 research, which identified a need to further investigate fatigue management in renal disease(14).  
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5 Two patients were involved as key informants in the development of the intervention under  
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7 study, providing consultation and feedback on the first intervention prototype through a series of  
8  
9 individual interviews that led to several program modifications (eg. clarification of key content;  
10  
11 simplification of design features). Two patients were also consulted about the control condition  
12  
13 to be used in this study, and their feedback led to modifications such as individualization of the  
14  
15 content material for specific patient interests and needs. Our current study team includes a  
16  
17 patient partner who will be consulted about patient-related issues that arise during the study, the  
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19 interpretation of results, and strategies to optimize dissemination and uptake.  
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## 24 25 **ETHICAL CONSIDERATIONS**

### 26 27 28 **Risks and Benefits**

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30 As part of their baseline assessment, participants will complete the PHQ-2 depression screening  
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32 assessment. This assessment may identify individuals who have, or are at risk for, clinical  
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34 depression. Any individual who scores >2 on the PHQ-2 will be offered connection to support  
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36 services, such as referral to their clinical social worker, or to a local counselling centre. Study  
37  
38 participants will also have to complete several study questionnaires, and participate in PEP  
39  
40 program treatment sessions. There is a risk that patients may experience short-term fatigue, or,  
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42 uncomfortable or unpleasant emotions in response to some of the questions in the study  
43  
44 questionnaires. Participants will therefore be advised that they can skip any questions or study  
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46 procedures that make them uncomfortable.  
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52 Direct benefits of participating are those which may be gained from completing the study  
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54 intervention, such as improved fatigue management, improved knowledge about kidney disease,  
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3 and/or and increased staff attention. Indirect benefits include the potential that others with kidney  
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5 disease may benefit from the study findings in the future.  
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### 8 9 **Data Safety and Monitoring Board (DSMB)**

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11 As the proposed study is small and its risks to participants are low, a DSMB is not needed.  
12  
13 Monitoring for potential risks (eg. fatigue, discomfort) will be performed by those interacting  
14  
15 directly with the patient during the study (the study clinicians and assessor). If any unexpected  
16  
17 concerns arise that cannot be immediately mitigated, the concerns will be brought forth to the PIs  
18  
19 for further discussion and decision-making.  
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### 23 **Research Ethics Approval**

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25 Ethics approval for the study has been obtained from the Conjoint Health Research Ethics Board  
26  
27 (CHREB) at the University of Calgary.  
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### 31 **DISSEMINATION PLAN**

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35 Trial results will be disseminated to patients with a summary sheet that will outline the trial  
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37 findings in lay language. Results will be disseminated to healthcare professionals and researchers  
38  
39 via publication in an academic journal and presentation at academic conferences.  
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### 43 **DISCUSSION**

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46 Fatigue is a common and disabling symptom of end-stage renal disease(1,4–6), that has  
47  
48 traditionally been challenging to mitigate due to its complex and nonspecific etiology. Results  
49  
50 from patient-reported outcome and engagement studies have highlighted the need to continue to  
51  
52 explore new fatigue management interventions for people with ESRD(5,14). Energy  
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54 management education (EME) is an approach that has been associated with positive fatigue-  
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3 related outcomes in other chronic disease populations. For example, in people with MS, RCTs  
4 have found that EME reduces patient fatigue and its impact on physical, cognitive and  
5 psychosocial functioning, and improves self-efficacy(20–22,38,39). Earlier-phase studies in  
6 acquired brain injury(40), cardiac disease(23,24), and post-polio(41) have similarly shown  
7 positive effects on fatigue and other related, high-priority outcomes, such as life participation  
8 (23,40). Furthermore, single-case studies conducted in a small sample of ESRD patients have  
9 generated promising findings regarding the effects of the PEP program on fatigue and life  
10 participation in people on chronic dialysis (25), suggesting this approach has potential to fill an  
11 important gap in ESRD care. However, studies in ESRD have thus far lacked important design  
12 elements, such as blinding, randomization, and sample representativeness, leaving the true  
13 potential of the PEP program unclear.

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

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3 The proposed pilot RCT has a number of strengths. The program under investigation (the PEP  
4 program) has been tailored specifically to meet the needs of the ESRD population: it is designed  
5 to facilitate participation in meaningful activities, which is a high priority for ESRD patients, and  
6 is delivered in a flexible format to accommodate the dialysis schedule. Patients have also been  
7 consulted and provided input at several stages of intervention development and testing. The  
8 study protocol was developed using the SPIRIT guidelines for a pilot RCT protocol, increasing  
9 the likelihood that important study design elements have been addressed. We have also  
10 developed a standardized training and administration protocol for the PEP program, that we  
11 anticipate will maximize treatment fidelity and consistency across program administrators. An  
12 active control condition to blind patients to their treatment allocation status will further increase  
13 the confidence in our study findings, by controlling for the placebo effect.  
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31 Our study also has limitations. First, we are excluding non-English speaking patients from the  
32 study, which limits its generalizability to non-English-speaking ESRD populations. However, the  
33 findings from this study may help to justify developing program materials in alternative  
34 languages that are accessible to a wider range of renal patients. We are also excluding patients  
35 outside of the in-center hemodialysis population who also experience a high burden of fatigue  
36 (eg. predialysis patients, peritoneal dialysis patients, home hemodialysis patients). This study  
37 should be viewed as an important first step in establishing the potential for the PEP program, that  
38 can lay the groundwork for future research into energy management education in other renal  
39 populations. Finally, we are unable to blind treatment administrators to treatment allocation, due  
40 to our inability to conceal which study condition is the treatment condition. We perceive blinding  
41 to be unfeasible because treatment administrators would be able to identify the treatment  
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3 condition, based on inequities between the two conditions in the amount of content dedicated to  
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5 fatigue and the length of time spent on staff training. The infeasibility of blinding is a well-  
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7 recognized limitation of trials studying psychosocial or behavioural interventions that are not  
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9 easily matched with an equivalent control.  
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15 In conclusion, the findings from this pilot RCT will further our understanding of a program that  
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17 has potential to address the challenging problem of fatigue in the ESRD patient population.  
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## 21 **TRIAL STATUS**

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24 The study started recruitment at the end of February 2019. Recruitment will continue until  
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26 August 2019. Data collection will conclude in January 2020.  
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## 29 **AUTHOR CONTRIBUTIONS**

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32  
33 Dr. Janine Farragher and Dr. Brenda Hemmelgarn led the design and writing of the pilot RCT  
34  
35 protocol. Dr. Chandra Thomas and Dr. Braden Manns helped with the development of the  
36  
37 participant identification plan, and provided advice on other key study issues. Dr. Pietro Ravani  
38  
39 and Dr. Meghan Elliott contributed feedback on trial design. All authors contributed important  
40  
41 intellectual content to the written protocol and approved the final version for publication.  
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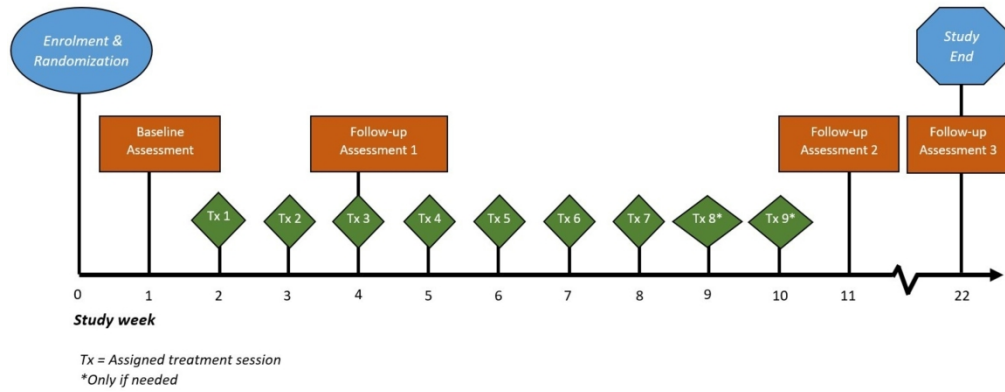
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3 **FIGURE LEGENDS**  
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6 Figure 1: Participant Timeline  
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### Participant Timeline

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	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	3

1	Trial registration:	<a href="#">#2b</a>	All items from the World Health Organization Trial	N/A
2				
3	data set		Registration Data Set	
4				
5				
6	Protocol version	<a href="#">#3</a>	Date and version identifier	1
7				
8				
9	Funding	<a href="#">#4</a>	Sources and types of financial, material, and other	4
10			support	
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14				
15	Roles and	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	1 & 21
16	responsibilities:			
17				
18	contributorship			
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22	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	N/A
23	responsibilities:			
24				
25	sponsor contact			
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27	information			
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31				
32	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study	N/A
33	responsibilities:		design; collection, management, analysis, and	
34			interpretation of data; writing of the report; and the	
35	sponsor and funder		decision to submit the report for publication, including	
36			whether they will have ultimate authority over any of	
37			these activities	
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47	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the	N/A
48	responsibilities:		coordinating centre, steering committee, endpoint	
49			adjudication committee, data management team, and	
50	committees		other individuals or groups overseeing the trial, if	
51			applicable (see Item 21a for data monitoring committee)	
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1	Background and	<a href="#">#6a</a>	Description of research question and justification for	5
2				
3	rationale		undertaking the trial, including summary of relevant	
4				
5			studies (published and unpublished) examining benefits	
6				
7			and harms for each intervention	
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11	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	10
12				
13	rationale: choice of			
14				
15	comparators			
16				
17				
18	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	7
19				
20				
21				
22	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg,	7
23				
24			parallel group, crossover, factorial, single group),	
25				
26			allocation ratio, and framework (eg, superiority,	
27				
28			equivalence, non-inferiority, exploratory)	
29				
30				
31	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic,	7
32				
33			academic hospital) and list of countries where data will	
34				
35			be collected. Reference to where list of study sites can	
36				
37			be obtained	
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41	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If	Table 1
42				
43			applicable, eligibility criteria for study centres and	
44				
45			individuals who will perform the interventions (eg,	
46				
47			surgeons, psychotherapists)	
48				
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51	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow	9
52				
53	description		replication, including how and when they will be	
54				
55			administered	
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1	Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated	Table 4
2				
3	modifications		interventions for a given trial participant (eg, drug dose	
4			change in response to harms, participant request, or	
5			improving / worsening disease)	
6				
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11	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention	10
12				
13	adherence		protocols, and any procedures for monitoring adherence	
14			(eg, drug tablet return; laboratory tests)	
15				
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19	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are	11
20			permitted or prohibited during the trial	
21	concomitant care			
22				
23				
24	Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the	11
25			specific measurement variable (eg, systolic blood	
26			pressure), analysis metric (eg, change from baseline,	
27			final value, time to event), method of aggregation (eg,	
28			median, proportion), and time point for each outcome.	
29			Explanation of the clinical relevance of chosen efficacy	
30			and harm outcomes is strongly recommended	
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41	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any	Figure 1
42			run-ins and washouts), assessments, and visits for	
43			participants. A schematic diagram is highly	
44			recommended (see Figure)	
45				
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51	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve	16
52			study objectives and how it was determined, including	
53			clinical and statistical assumptions supporting any	
54			sample size calculations	
55				
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1	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment	16
2			to reach target sample size	
3				
4				
5				
6	Allocation: sequence	<a href="#">#16a</a>	Method of generating the allocation sequence (eg,	8
7	generation		computer-generated random numbers), and list of any	
8			factors for stratification. To reduce predictability of a	
9			random sequence, details of any planned restriction (eg,	
10			blocking) should be provided in a separate document	
11			that is unavailable to those who enrol participants or	
12			assign interventions	
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23	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence	8
24	concealment		(eg, central telephone; sequentially numbered, opaque,	
25			sealed envelopes), describing any steps to conceal the	
26	mechanism		sequence until interventions are assigned	
27				
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33	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will	8
34	implementation		enrol participants, and who will assign participants to	
35			interventions	
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41	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions	8
42			(eg, trial participants, care providers, outcome	
43			assessors, data analysts), and how	
44				
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48	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	N/A
49	emergency		permissible, and procedure for revealing a participant's	
50			allocated intervention during the trial	
51	unblinding			
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1	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome,	11
2			baseline, and other trial data, including any related	
3			processes to promote data quality (eg, duplicate	
4			measurements, training of assessors) and a description	
5			of study instruments (eg, questionnaires, laboratory	
6			tests) along with their reliability and validity, if known.	
7				
8			Reference to where data collection forms can be found,	
9			if not in the protocol	
10				
11	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete	Table 4
12	retention		follow-up, including list of any outcome data to be	
13			collected for participants who discontinue or deviate from	
14			intervention protocols	
15				
16	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage,	13
17			including any related processes to promote data quality	
18			(eg, double data entry; range checks for data values).	
19			Reference to where details of data management	
20			procedures can be found, if not in the protocol	
21				
22	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary	15
23			outcomes. Reference to where other details of the	
24			statistical analysis plan can be found, if not in the	
25			protocol	
26				
27	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and	N/A
28	analyses		adjusted analyses)	
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1	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	16
2				
3	population and		adherence (eg, as randomised analysis), and any	
4				
5	missing data		statistical methods to handle missing data (eg, multiple	
6				
7			imputation)	
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11	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC);	18
12				
13	formal committee		summary of its role and reporting structure; statement of	
14				
15			whether it is independent from the sponsor and	
16			competing interests; and reference to where further	
17			details about its charter can be found, if not in the	
18			protocol. Alternatively, an explanation of why a DMC is	
19			not needed	
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28	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping	N/A
29				
30	interim analysis		guidelines, including who will have access to these	
31				
32			interim results and make the final decision to terminate	
33				
34			the trial	
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38	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing	N/A (low-
39				risk trial)
40			solicited and spontaneously reported adverse events	
41				
42			and other unintended effects of trial interventions or trial	
43				
44			conduct	
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48	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if	N/A
49				
50			any, and whether the process will be independent from	
51				
52			investigators and the sponsor	
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55	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee /	18
56				
57	approval		institutional review board (REC / IRB) approval	
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1	Protocol	<a href="#">#25</a>	Plans for communicating important protocol	14
2				
3	amendments		modifications (eg, changes to eligibility criteria,	
4			outcomes, analyses) to relevant parties (eg,	
5			investigators, REC / IRBs, trial participants, trial	
6			registries, journals, regulators)	
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13	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from	7
14			potential trial participants or authorised surrogates, and	
15			how (see Item 32)	
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21	6Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	N/A
22			participant data and biological specimens in ancillary	
23	ancillary studies		studies, if applicable	
24				
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28	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	13
29			participants will be collected, shared, and maintained in	
30			order to protect confidentiality before, during, and after	
31			the trial	
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38	Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	4
39			investigators for the overall trial and each study site	
40	interests			
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44	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial	N/A
45			dataset, and disclosure of contractual agreements that	
46			limit such access for investigators	
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51	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	N/A
52			compensation to those who suffer harm from trial	
53	trial care		participation	
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1	Dissemination	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	18
2				
3	policy: trial results		results to participants, healthcare professionals, the	
4			public, and other relevant groups (eg, via publication,	
5			reporting in results databases, or other data sharing	
6			arrangements), including any publication restrictions	
7				
8	Dissemination	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	N/A
9				
10	policy: authorship		professional writers	
11				
12	Dissemination	<a href="#">#31c</a>	Plans, if any, for granting public access to the full	N/A
13				
14	policy: reproducible		protocol, participant-level dataset, and statistical code	
15				
16	research			
17				
18	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation	Appendix
19				
20	materials		given to participants and authorised surrogates	
21				
22	Biological	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
23				
24	specimens		biological specimens for genetic or molecular analysis in	
25			the current trial and for future use in ancillary studies, if	
26			applicable	
27				

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43 BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool made  
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