PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	PROTOCOL FOR A PILOT RANDOMIZED CONTROLLED TRIAL OF AN EDUCATIONAL PROGRAM FOR ADULTS ON CHRONIC HEMODIALYSIS WITH FATIGUE (FATIGUE-HD)
AUTHORS	Farragher, Janine; Thomas, Chandra; Ravani, P; Manns, Braden; Elliott, Meghan; Hemmelgarn, Brenda

VERSION 1 – REVIEW

REVIEWER	Federica Picariello King's College London, UK
REVIEW RETURNED	17-Mar-2019

GENERAL COMMENTS	Protocol for a pilot randomized controlled trial of an educational program for adults on chronic hemodialysis with fatigue (fatigue-HD). BMJ Open. Review comments This is a protocol of a randomised controlled trial evaluating the feasibility of an energy management programme for fatigue in haemodialysis. Fatigue has been identified as a core outcome in haemodialysis according to the SONG initiative so development of a fatigue management pathway in this setting is obviously necessary. There were a couple of important issues in the manuscript that would require revision before this manuscript is of publishable standard. Abstract: The fatigue cut-off on the FSS was mentioned in the methods section, so this needs to be stated here, instead of the vague statement in relation to moderate or severe fatigue based on routine reporting. Introduction: You mentioned that fatigue is common in this setting, how common? An estimate of prevalence would be valuable here. Here you could also mention the evidence on the association between fatigue and clinical outcomes in this patient population. Overall, the introduction requires further work, particularly to demonstrate the theoretical basis for the EME intervention. It would be important to present a biopsychosocial perspective of fatigue developed in other long-term physical conditions, and how this could be relevant here. The relevance of the EME intervention needs to be a lot clearer and this would provide a better link between the first and second paragraphs of the introduction. Merely mentioning depression and sleep disorders when referring to psychological/behaviour factors is over-simplistic, beliefs, emotions, and coping behaviours should be mentioned instead. Additionally, there is more evidence in support of the role of sleep quality in fatigue, rather than sleep disorders per se (e.g. Jhamb, M., Liang, K., Yabes, J., Steel, J. L., Dew, M. A., Shah, N., & Unruh, M.

	(2013). Prevalence and correlates of fatigue in chronic kidney disease and end-stage renal disease: are sleep disorders a key to understanding fatigue?. American Journal of Nephrology, 38(6), 489-495; Unruh, M. L., Buysse, D. J., Dew, M. A., Evans, I. V., Wu, A. W., Fink, N. E., . . . Study, C. (2006). Sleep quality and its correlates in the first year of dialysis. Clinical Journal of the American Society of Nephrology, 1(4), 802-810). Elaborating on the theoretical basis of fatigue would also be helpful in terms of a discussion of the mechanisms behind any improvements in fatigue following the EME intervention. You need to build a strong rationale for why an EME intervention would be most appropriate here, above other pharmacological and non-pharmacological interventions. Why pharmacological management or exercise are not always appropriate should be articulated further (i.e. ESA management ->ceiling effects, exercise contraindications). Preliminary work on the usability and acceptability of the intervention has been mentioned, is this work published? It would be helpful to know about this, i.e. how was this evaluated etc.? Methods: Referring to the trial as feasibility may be more appropriate, as your primary objective relates to feasibility. Please see this NIHR guidance on the differences between feasibility and pilot trials https://www.nihr.ac.uk/funding-and-support/documents/funding-for-research-studies/research-programmes/PGfAR/Feasibility%20and%20Pilot%20studies.pdf The fatigue cut-off on the FSS needs to be clarified. Is this based on previous research? How was this cut-off identified? This needs to be justified. The selection of the instruments needs to be justified further, particularly in light of recent evidence (Ju, A, Unruh, M, Davison, S, Dapueto, J, Dew, MA, Fluck, R, Germain, M, Jassal, V, Obrador, G, O'Donoghue, D, Josephson, M, Craig, JC, Viecelli, A, O'Lone, E, Hanson, CS, Manns, B, Sautenet, B, Howell, M, & Tong, A for the SONG-HD Workshop Investigators. (2018). Establishing a core outcome measure for fatigue in patients on hemodialysis: a standardised outcomes in nephrology – hemodialiysis (SONG-HD) consensus workshop report. American Journal of Kidney Disease, 72(1), 104-112). In relation to the exclusion criteria, will patients receiving psychotherapy or physiotherapy be excluded, as this may lead to contamination? Will the same facilitators deliver the PEP program and the active control? This was not sufficiently clear from the manuscript. What will the program workbook consist of? How was the intervention tailored specifically to meet the needs of this patient population? Examples of this would be helpful. What training will the facilitators receive in terms of duration and number of training sessions? Will there be a minimum therapy dose, or will this be determined as part of the trial? It would be helpful if all data collected at each time point were presented in a table. What lab data will be collected at follow-up? No process variables will be collected as part of this study, and the potential mechanisms of the intervention were not articulated in the manuscript, yet this is a key aspect of development of complex interventions based on the MRC guidelines. Even though a formal process analysis is outside of the scope of a feasibility or pilot trial, such considerations are necessary ahead of a full-scale definitive trial.

	The sample size is insufficiently defined, it would be important to state the anticipated number of patients that will be eligible and are likely to consent, providing rates with margins of error. A flow diagram of the anticipate flow of participants through the study should also be presented to visually summarise the various steps of the study. The analysis section was clear and concise. In the PPI section, it would be important to state how many service users were consulted and in what format when developing this intervention. It would also be valuable here to provide an example of the changes made to the intervention based on feedback from service users, to demonstrate how their feedback was integrated and their voices taken into account. In relation to assessment of risk, how will suicide risk be managed? At the end of the protocol, you need to state the current stage of the study. The dates of the study should be included in the protocol. Discussion: Is there a systematic review of EME interventions for fatigue? Again, the preliminary findings mentioned need to be elaborated further, as also mentioned in my comments earlier. When discussing the limitations, it may be helpful to also consider implementation potential. You could also mention here how widespread access to the internet is in this patient population. A feasibility trial of an online psychological intervention for distress in the UK found that low computer literacy was the biggest obstacle to uptake of the intervention (Hudson, J. L., Moss-Morris, R., Norton, S., Picariello, F., Game, D., Carroll, A., ... & Chilcot, J. (2017). Tailored online cognitive behavioural therapy with or without therapist support calls to target psychological distress in adults receiving haemodialysis: a feasibility randomised controlled trial. Journal of psychosomatic Research, 102, 61-70). This needs to be considered here. I am surprised that this trial does not include a nested qualitative study to further explore acceptability and identify any aspects in need of revision. It would be helpful if the title was more specific in relation to the intervention, instead of referring to the intervention as “an educational program”.

REVIEWER	Zhiguo Mao Division of Nephrology, Shanghai Changzheng Hospital, Second Military Medical Universtiy, Shanghai, China
REVIEW RETURNED	24-Mar-2019

GENERAL COMMENTS	This is a well-designed RCT protocol to estimate trial eligibility, inform the primary outcome measure and sample size, and evaluate fidelity among program administrators, so as to testify the efficacy an educational program which was developed to manage fatigue in maintaining hemodialysis patients. The methods are corret and outcomes clearly defined. The research ethics are appropriately addressed and the results will answer the study objetives.

REVIEWER	Dr Chloe Grimmett University of Southampton, UK
REVIEW RETURNED	10-Jun-2019

GENERAL COMMENTS	Thank for you for the opportunity to review this protocol paper. This is a very well written manuscript that describes an intervention designed to support adults receiving chronic haemodialysis who are experiencing fatigue. It is a strength of this paper that the objectives of the study are driven by input and preferences from service users. Please see some minor points for consideration. Abstract: May I suggest a brief expansion of the concept of 'life participation' in the abstract for those not familiar with this area. The authors state patients may feel 'discomfort' while filling out the questionnaire. This sounds ambiguous, i.e. is this physical or emotional? Please clarify. Introduction: Page 6 line 8. The authors state 'several single-case' studies found….Suggest specifying how many. Additionally provide further details of scale and definition of 'small to moderate' decrease in fatigue and disability. Page 6, line 55 the phrase 'maintenance of short-term effects' is a little confusing, as to maintain something short term sounds contradictory, suggest re-phrase. Objectives: "Objective 2 To explore maintenance of gains in fatigue". Again, I find this difficult to interpret as decline in fatigue is the preferred outcome. Methods: Please can the authors justify the inclusion criteria as per the Fatigue Severity Scale. Why was this particular measure chosen and what is the justification for this particular cut-off point? Authors describe the program will be delivered over 7-9 weeks. It is unclear where the lower value of 7weeks is derived from. Can the authors clarify or alternatively perhaps describe the intervention as a maximum of 9 weeks with a minimum adherence cut off? The authors state that questionnaires will be filled in either before, during or after dialysis. Is time of completion likely to impact on results? For example, might patients feel more of less fatigue at different time points? The authors highlight the inclusion of several different measures of fatigue in order to determine the most appropriate outcome measure for a fully powered trial. Are patients warned that questionnaire items will be repetitive? Have the authors considered any measures to minimise missing data due to this? Please can the authors clarify the extent of fidelity checks being conducted? The manuscript states that all sessions will be audio-recorded but presumably there is not capacity to run checks on all of these? Page 15 line 23 the authors state that 'a sample of the audio recordings will be…transcribed' but don't state how many or for what purpose. Discussion: There is some overlap between literature cited in the discussion and the intro. Suggest authors limit duplication. Finally, the authors note that recruitment and retention of patients is likely to be challenging. Have there been any measures put in place to try and minimise this? I wish the authors the best of luck with this much needed trial.

VERSION 1 – AUTHOR RESPONSE

Responses to Reviewer Comments
Reviewer 1

Abstract

1. The fatigue cut-off on the FSS was mentioned in the methods section, so this needs to be stated here, instead of the vague statement in relation to moderate or severe fatigue based on routine reporting.

Thank you for this suggestion. We have changed the sentence accordingly in the abstract:

"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."

Introduction:

2. You mentioned that fatigue is common in this setting, how common? An estimate of prevalence would be valuable here.

Thank you for this suggestion; we have added a prevalence estimate into the introduction:

"Fatigue is a pervasive symptom of end-stage renal disease (ESRD) experienced by an estimated 7 in 10 people on maintenance dialysis therapy."

3. Here you could also mention the evidence on the association between fatigue and clinical outcomes in this patient population.

Thank you for this suggestion. We have added this into the abstract:

"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."

Introduction

4. Overall, the introduction requires further work, particularly to demonstrate the theoretical basis for the EME intervention. It would be important to present a biopsychosocial perspective of fatigue developed in other long-term physical conditions, and how this could be relevant here. The relevance of the EME intervention needs to be a lot clearer and this would provide a better link between the first and second paragraphs of the introduction. Merely mentioning depression and sleep disorders when referring to psychological/behavior factors is over-simplistic, beliefs, emotions, and coping behaviours should be mentioned instead. Additionally, there is more evidence in support of the role of sleep quality in fatigue, rather than sleep disorders per se (e.g. Jhamb, M., Liang, K., Yabes, J., Steel, J. L., Dew, M. A., Shah, N., & Unruh, M. (2013). Prevalence and correlates of fatigue in chronic kidney disease and end-stage renal disease: are sleep disorders a key to understanding fatigue? American Journal of Nephrology, 38(6), 489-495; Unruh, M. L., Buysse, D. J., Dew, M. A., Evans, I. V., Wu, A. W., Fink, N. E., . . . Study, C. (2006). Sleep quality and its correlates in the first year of dialysis. Clinical Journal of the American Society of Nephrology, 1(4), 802-810). Elaborating on the theoretical basis of fatigue would also be helpful in terms of a discussion of the mechanisms behind any improvements in fatigue following the EME intervention. You need to build a strong rationale for why

an EME intervention would be most appropriate here, above other pharmacological and nonpharmacological interventions.

Thank you for this feedback. We have added additional detail throughout the introduction about the theory of fatigue in ESRD, and clarified the theoretical basis behind the intervention (see manuscript for revisions made).

5. Why pharmacological management or exercise are not always appropriate should be articulated further (i.e. ESA management ->ceiling effects, exercise contraindications).

Thank you for this suggestion; this has been articulated further in the introduction:

“These approaches, while efficacious for some patients, also have limitations. For example, Erythropoeitin therapy does not address the multiple fatigue mechanisms in ESRD beyond anemia, while exercise training has been challenging to implement and sustain in ESRD clinical practice, due to factors such as insufficient staff expertise and low patient motivation.”

6. Preliminary work on the usability and acceptability of the intervention has been mentioned, is this work published? It would be helpful to know about this, i.e. how was this evaluated etc.?

Thank you for this inquiry. We have added a citation to the published thesis on this work, and have included additional data about these studies in the introduction:

“Preliminary acceptability testing found that the program was both practical and well-received based on feedback from patient interviews, while five single-case studies showed small to moderate improvements in fatigue and life participation associated with the program in people with ESRD (based on Tau-U effect-size estimates and in-depth patient interviews).”

Methods:
7. Referring to the trial as feasibility may be more appropriate, as your primary objective relates to feasibility. Please see this NIHR guidance on the differences between feasibility and pilot studies: https://www.nihr.ac.uk/funding-and-support/documents/funding-for-researchstudies/research-programmes/PGfAR/Feasibility%20and%20Pilot%20studies.pdf
Thank you for this suggestion. We do appreciate that our study has a feasibility component; however, we believe that the study best meets the definition of a pilot study. The NIHR states that feasibility studies “may not themselves be randomised. Crucially, feasibility studies do not evaluate the outcome of interest; that is left to the main study.” Our study does include randomization and measures of the outcomes of interest. By contrast, the NIHR states that a pilot study “is focused on the processes of the main study, for example to ensure recruitment, randomisation, treatment, and follow-up assessments all run smoothly. It will therefore resemble the main study in many respects, including an assessment of the primary outcome.” Others have similarly clarified that: “a feasibility study asks whether something can be done, should we proceed with it, and if so, how. A pilot study asks the same questions but also has a specific design feature: in a pilot study a future study, or part of a future study, is conducted on a smaller scale.” (Eldridge, Lancaster, Campbell, Thabane, Hopewell, Coleman, Bond. (2014). Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework.) Given that our study assesses feasibility but is also a smaller-scale replication of all aspects of the future RCT to be conducted (including randomization and measurement of the primary outcome), we purport that it most closely resembles the definition of a pilot study.
8. The fatigue cut-off on the FSS needs to be clarified. Is this based on previous research? How was this cut-off identified? This needs to be justified.

Thank you for this inquiry. A Fatigue Severity Scale score of ≥4 has previously been used to screen for patient eligibility in energy management education studies from other populations (eg. Multiple Sclerosis). For the purposes of our study, however, the issue of greatest interest to determine patient appropriateness for the intervention (and therefore study) is the extent of the effect of fatigue on the patient's life participation (ie. ability to participate in valued day to day activities). Items 5,7,8 and 9 of the FSS directly inquire about this issue; thus, rather than having the patient fill out the whole questionnaire, we chose to use these 4 items to screen for study eligibility.

9. The selection of the instruments needs to be justified further, particularly in light of recent evidence (Ju, A, Unruh, M, Davison, S, Dapueto, J, Dew, MA, Fluck, R, Germain, M, Jassal, V, Obrador, G, O'Donoghue, D, Josephson, M, Craig, JC, Viecelli, A, O'Lone, E, Hanson, CS, Manns, B, Sautenet, B, Howell, M, & Tong, A for the SONG-HD Workshop Investigators. (2018). Establishing a core outcome measure for fatigue in patients on hemodialysis: a standardised outcomes in nephrology – hemodialiysis (SONG-HD) consensus workshop report. American Journal of Kidney Disease, 72(1), 104-112).
Thank you for this suggestion. We have added a sentence to justify the selection of questionnaires for this study based on the SONG-HD findings:
"The following questionnaires will be used to measure fatigue and life participation outcomes. These questionnaires were selected based on patient-reported priorities such as minimizing the burden of administration, limiting the recall period, and capturing the impact of fatigue on life participation."

10. In relation to the exclusion criteria, will patients receiving psychotherapy or physiotherapy be excluded, as this may lead to contamination?
Given that many patients in our setting participate in other interventions such as intradialytic exercise, and that this EME program is intended to supplement, not replace, existing interventions, there is no exclusion criteria around participating in other fatigue interventions. The RCT design of the study should balance participation in such co-interventions between treatment arms and therefore prevent bias in the study results.

11. Will the same facilitators deliver the PEP program and the active control? This was not sufficiently clear from the manuscript.
Yes, the same facilitators will deliver the PEP program and active control. A clarifying statement has been added to the protocol:
"Treatment administrators will undergo training in the treatment and control protocols, and will each be responsible for providing both treatments."

12. What will the program workbook consist of?
The program workbook is a minor supplementary part of the program. It provides instructions about the program (eg. how to access the computer modules); space for participants to complete activities outlined in the modules; and a brief summary of key educational content provided in the modules.

13. How was the intervention tailored specifically to meet the needs of this patient population? Examples of this would be helpful.
Thank you for this inquiry. This has been further clarified in the introduction, as follows:
"We developed a personalized, web-supported EME program (the "PEP" Program), that has been tailored for the ESRD population in several ways. The program is designed specifically to target the impact of fatigue on life participation, in accordance with patient-identified priorities, by using a personalized, goal-focused intervention approach. It is also delivered in a concise, flexible, and web-supported format, to accommodate patients' time restrictions resulting from their dialysis schedules."

14. What training will the facilitators receive in terms of duration and number of training sessions?

Thank you for this inquiry. The facilitators underwent three formal training sessions lasting approximately 1.5 hours each. This has been clarified in the protocol:
"Training for the treatment protocol will consist of three 90 minute sessions, while control protocol training will include one 60 minute session."

15. Will there be a minimum therapy dose, or will this be determined as part of the trial?
Thank you for this inquiry. The minimum therapy dose is 7 treatment sessions. This dose was decided in consultation with those who designed the problem-solving framework (CO-OP) used in the program, who agreed that a minimum of 7 treatment sessions would be necessary for patients to feasibly make progress on three personal goals. This dose was also confirmed as being adequate by participants in the early-phase testing of the program.

16. It would be helpful if all data collected at each time point were presented in a table.
Thank you for this suggestion. Unfortunately, we are already at the maximum number of tables and figures for a manuscript for BMJ open. However, we would be willing to comply with this request at the advice of the Editor.

17. What lab data will be collected at follow-up?
Serum hemoglobin and albumin will be collected at follow-up. This will allow the investigators to explore potential reasons for unexpected study results, if necessary (eg. differences in changes in hemoglobin levels or kidney functioning between the 2 treatment groups during the study). This detail has been added to the protocol:
"Follow-up information (including recent hospitalizations, illnesses, dialysis changes, exercise changes, serum hemoglobin and albumin) will be documented at each follow-up visit."

18. No process variables will be collected as part of this study, and the potential mechanisms of the intervention were not articulated in the manuscript, yet this is a key aspect of development of complex interventions based on the MRC guidelines. Even though a formal process analysis is outside of the scope of a feasibility or pilot trial, such considerations are necessary ahead of a full-scale definitive trial.
Thank you for this feedback. We do appreciate the need to understand and examine mechanisms of change in early-phase development and testing of a complex intervention. This program has undergone extensive preliminary development and testing that was in accordance with the MRC guidelines. In our preliminary studies, information about mechanisms of change associated with the program (eg. strategy use, learning, self-efficacy) was collected. These studies are currently under review with other peer-review journals. They are also published as part of a completed doctoral thesis about the program development (Farragher, 2018, Developing "PEP": A Personalized, Web-Supported Energy Conservation Education Program for People on Chronic Dialysis Therapy with Fatigue).

19. The sample size is insufficiently defined, it would be important to state the anticipated number of patients that will be eligible and are likely to consent, providing rates with margins of error.
Thank you for this suggestion. We recognize that there are many suggested approaches for identifying a sample size for a pilot study. We have based our sample size calculation on the recommendations of Whitehead et al., 2016 (Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable). We have also included estimates of eligibility and recruitment rates for the pilot RCT, to demonstrate feasibility.

20. A flow diagram of the anticipate flow of participants through the study should also be presented to visually summarise the various steps of the study.

Thank you for this suggestion. Information about participant flow through the study is included in the participant timeline in Figure 1.

21. The analysis section was clear and concise.
Thank you for this feedback.

22. In the PPI section, it would be important to state how many service users were consulted and in what format when developing this intervention. It would also be valuable here to provide an example of the changes made to the intervention based on feedback from service users, to demonstrate how their feedback was integrated and their voices taken into account.
Thank you for this feedback. We have included additional detail and examples of patient involvement in the program development process.

23. In relation to assessment of risk, how will suicide risk be managed?
We have no protocols for managing suicide risk specifically for this study. However, as per our study protocol (which has been approved by the Conjoint Health Research Ethics Board), we will address risk for depression in the following way:
As part of the baseline data collection procedures, participants will complete the PHQ-2 depression screening assessment. This assessment may identify individuals who have, or are at risk for, clinical depression. The PHQ-2 specifies that individuals with a score of >2 on the measure should be further evaluated for clinical depression. As such, any individual who scores >2 on the PHQ-2 during the study screening procedures will be offered connection to support services, such as referral to their clinical social worker, or to the Calgary Counselling Centre at 403-691- 5991 or http://www.calgarycounselling.com/.

24. At the end of the protocol, you need to state the current stage of the study. The dates of the study should be included in the protocol.
Thank you for this suggestion. We have added information on trial dates and status into the protocol: "The study started recruitment at the end of February 2019. Recruitment will continue until August 2019. Data collection will conclude in January 2020."

Discussion
25. Is there a systematic review of EME interventions for fatigue?
There is one systematic review conducted specifically in Multiple Sclerosis (Blikman et al, 2013, Effectiveness of energy conservation treatment in reducing fatigue in multiple sclerosis: a systematic review and meta-analysis). We have also conducted a scoping review of EME interventions across chronic disease populations that is currently under review with an academic journal and is published as part of a doctoral thesis about the program development. (Farragher, 2019, Developing "PEP": A Personalized, Web-Supported Energy Conservation Education Program for People on Chronic Dialysis Therapy with Fatigue).

26. Again, the preliminary findings mentioned need to be elaborated further, as also mentioned in my comments earlier.
Thank you for this suggestion. We have included additional detail about the preliminary findings in the introduction and discussion, as described in revision #6.

27. When discussing the limitations, it may be helpful to also consider implementation potential. You could also mention here how widespread access to the internet is in this patient population. A feasibility trial of an online psychological intervention for distress in the UK found that low computer literacy was the biggest obstacle to uptake of the intervention (Hudson, J. L., Moss-Morris, R., Norton, S., Picariello, F., Game, D., Carroll, A., ... & Chilcot, J. (2017). Tailored online cognitive behavioural therapy with or without therapist support calls to target psychological distress in adults receiving

haemodialysis: a feasibility randomised controlled trial. Journal of psychosomatic Research, 102, 61-70). This needs to be considered here.
Thank you for this feedback. Our intervention was designed with different individual patient needs and abilities in mind. Individuals without access to the internet can complete the program modules in the dialysis unit during dialysis sessions, provided there is an iPad or laptop computer available for use. The program requires little to no computer literacy to successfully navigate, as demonstrated in our preliminary usability testing – instructions for accessing the modules are clear and explicit, and the modules themselves are simple and intuitive to navigate, which was achieved through usability testing and design revisions. The program was subsequently found to be usable even among patients who reported never using computers otherwise. However, patients who are still uncomfortable accessing and completing the modules independently could feasibly receive support to access the modules from staff in the dialysis unit.

28. I am surprised that this trial does not include a nested qualitative study to further explore acceptability and identify any aspects in need of revision.
Thank you for this suggestion. We have also since recognized the benefit of exploring patient perceptions of the study and program. We are therefore in the process of designing a qualitative investigation to supplement the findings of this pilot RCT.

29. It would be helpful if the title was more specific in relation to the intervention, instead of referring to the intervention as “an educational program”.
Thank you for this suggestion. Because patients are being blinded as to which educational program is the intervention vs. control condition in this study, we named the study in this way to maintain blinding on study materials (eg. informed consent form).

Reviewer 2

No changes requested.

Reviewer 3

Abstract:

30. May I suggest a brief expansion of the concept of ‘life participation’ in the abstract for those not familiar with this area.
Thank you for this suggestion. We have further clarified this concept in the abstract:
“Preliminary studies have demonstrated positive effects on fatigue and life participation (ie. the ability to participate in valued day-to-day activities)”

31. The authors state patients may feel ‘discomfort’ while filling out the questionnaire. This sounds ambiguous, i.e. is this physical or emotional? Please clarify.
Thank you for this suggestion. We have clarified in the abstract that we meant emotional discomfort:
“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.”

Introduction:
32. Page 6 line 8. The authors state ‘several single-case’ studies found….Suggest specifying how many. Additionally provide further details of scale and definition of ‘small to moderate’ decrease in fatigue and disability.

Thank you for this feedback. We have added further detail about these data, as outlined in revision #6.

33. Page 6, line 55 the phrase ‘maintenance of short-term effects’ is a little confusing, as to maintain something short term sounds contradictory, suggest re-phrase.
Thank you, we have reworded this sentence accordingly:
“Finally, we need to collect more data on the effects of the program on possible primary outcomes (fatigue and life participation) to determine the optimal primary outcome measure for an RCT, estimate the sample size for a an RCT, and establish longer-term effects of the PEP program on patient fatigue and life participation.”

Objectives:

34. “Objective 2 To explore maintenance of gains in fatigue”. Again, I find this difficult to interpret as decline in fatigue is the preferred outcome.
Thank you, we have reworded the objective in keeping with revision #33.

Methods:

35. Please can the authors justify the inclusion criteria as per the Fatigue Severity Scale. Why was this particular measure chosen and what is the justification for this particular cut-off point?
Thank you for this inquiry. Please see response #8 for an explanation.

36. Authors describe the program will be delivered over 7-9 weeks. It is unclear where the lower value of 7 weeks is derived from. Can the authors clarify or alternatively perhaps describe the intervention as a maximum of 9 weeks with a minimum adherence cut off?
Thank you for this inquiry. The program length is intentionally flexible, so it can be tailored to individual patient needs and rates of progress. Some patients might only require 7 sessions before they achieve their treatment goals or exhaust all possible energy management strategies, while others may take longer (eg. if their goals are more complex, or if they have a lower activity tolerance requiring shorter treatment sessions). We have modified the wording about this in the protocol to promote clarity:
“The program is delivered over 7-9 weekly sessions, dependent upon individual patient needs and rates of progress.”

37. The authors state that questionnaires will be filled in either before, during or after dialysis. Is time of completion likely to impact on results? For example, might patients feel more of less fatigue at different time points?
Thank you for this inquiry. Because the questionnaires ask patients to report on their average fatigue experienced over the past week or month, we do not anticipate the specific timing of questionnaires will significantly impact their answers.

38. The authors highlight the inclusion of several different measures of fatigue in order to determine the most appropriate outcome measure for a fully powered trial. Are patients warned that questionnaire items will be repetitive? Have the authors considered any measures to minimise missing data due to this?
Thank you for this inquiry. There is no explicit warning provided to patients that questionnaire items are repetitive. However, the questionnaires chosen for this study are relatively brief (eg the SF-36 includes 4 questions; the Fatigue Severity Scale consists of 9 questions), which was done to reduce participant burden in light of the fatigue experienced by people on dialysis. Thus, we do not anticipate extensive problems with questionnaire completion.

39. Please can the authors clarify the extent of fidelity checks being conducted? The manuscript states that all sessions will be audio-recorded but presumably there is not capacity to run checks on all of these? Page 15 line 23 the authors state that 'a sample of the audio recordings will be…transcribed' but don't state how many or for what purpose.
Thank you for this feedback. We are conducting treatment fidelity checks for the pilot study to determine the effectiveness of our staff training program. As such, we will be examining two treatment sessions per participant randomized to the treatment condition (ie. 40 sessions in total). This information has been clarified in the protocol:
"Two sessions per participant randomized to the treatment condition will then be randomly selected and used to evaluate treatment fidelity of the program administrators, according to the CO-OP fidelity checklist."
Treatment fidelity will be established using the CO-OP fidelity checklist, which includes 26 items, each scored on a scale of 0-5, that measure the extent of use of various key elements of the treatment approach by the treatment administrator. This information will be used to improve, if necessary, the training provided to staff about the treatment program by identifying areas of weakness in their training. This information is included under the "Data Collection" section of the protocol.

Discussion:

40. There is some overlap between literature cited in the discussion and the intro. Suggest authors limit duplication.
We appreciate the feedback, and have modified the discussion section accordingly to minimize repetition (see manuscript for revisions made).

41. Finally, the authors note that recruitment and retention of patients is likely to be challenging. Have there been any measures put in place to try and minimize this?
Thank you for this inquiry. We have primarily attempted to maximize recruitment and retention for the study by making the intervention under study as patient-centered as possible. In the initial stages of intervention development, we conducted a needs assessment to determine the needs and potential barriers of people on dialysis related to participating in an intervention like the PEP program. This informed several design features that were included in the intervention, such as short, concise treatment sessions, minimal "homework" or work outside of treatment sessions, and an individualized treatment approach used that focuses on patients' own high-priority life participation challenges. In addition, we attempted to minimize potential study-related barriers to participation, such as questionnaire burden, by selecting brief outcome questionnaires of fatigue or life participation. We believe these features will maximize our recruitment and retention rates for the study.
However, we will be able to determine this more conclusively with the data from this pilot RCT.

VERSION 2 – REVIEW

REVIEWER	Federica Picariello King's College London, United Kingdom
REVIEW RETURNED	24-Jun-2019

GENERAL COMMENTS	Thank you for making extensive changes to the manuscript based on the review comments. You clearly put a lot of effort into the revision. Just some minor points for you to address based on my previous comments: -You need to justify the FSS cut-off used, as usually a mean score of 4 or above is used to indicate clinically significant fatigue.

	-The sample size still needs to be more clearly defined. You can break down the justification into steps, i.e. XXX can be approached, out of these XXX will consent, out of the patients providing consent, XXX will be eligible. Make sure to use references to substantiate the estimates you are using. Please provide rates with margins of error. Overall, it is not entirely clear, whether the sample is estimated based on the small to medium effect (this needs to be defined based on previous research) or recruitment numbers?

REVIEWER	Dr Chloe Grimmett University of Southampton
REVIEW RETURNED	24-Jun-2019

GENERAL COMMENTS	Thank you to the authors for providing a thorough response to the queries presented. The authors provide an important account of the considerations made for participants during the development of the intervention to ensure acceptability is maximised. I suggest these are included in the manuscript

VERSION 2 – AUTHOR RESPONSE

Reviewer 3:

3. The authors provide an important account of the considerations made for participants during the development of the intervention to ensure acceptability is maximised. I suggest these are included in the manuscript.

Thank you for this feedback. We added the following into the manuscript's introduction during our last manuscript revision, that describes the elements we outlined to the reviewer about the program's design and acceptability:

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

Reviewer 1:

4. You need to justify the FSS cut-off used, as usually a mean score of 4 or above is used to indicate clinically significant fatigue.
Thank you for this feedback. We have added a sentence into the "Participant Identification" section to clarify this point:
"An average score of ≥4 on items 5, 7, 8 and 9 of the Fatigue Severity Scale is being used to identify eligible patients because these items ask about the impact of fatigue on life participation, which is the intended focus of the intervention."

5. The sample size still needs to be more clearly defined. You can break down the justification into steps, i.e. XXX can be approached, out of these XXX will consent, out of the patients providing consent, XXX will be eligible. Make sure to use references to substantiate the estimates you are using. Please provide rates with margins of error. Overall, it is not entirely clear, whether the sample is estimated based on the small to medium effect (this needs to be defined based on previous research) or recruitment numbers?

Thank you for this feedback, and our apologies for the lack of clarity. We have chosen a sample size that will provide sufficient accuracy in the effect size estimate to minimize the sample size required for a future RCT. Our choice was driven by the recommendations of Whitehead and colleagues (2016), who suggest that the ideal sample size for a pilot is 20 when a medium effect size is expected, and 40 when a small effect size is expected. We expect an effect size that is between small and medium based on our preliminary data about this intervention, and are therefore aiming to gather complete outcome data for 30 patients. Recruiting 40 patients will enable us to achieve this even if 25% of the participant pool drops out, which is a fairly conservative estimate.

We have revised the section in the protocol to promote further clarity:

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

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