PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Energy Conservation Education Intervention for People with End-stage Kidney Disease Receiving Haemodialysis (EVEREST): protocol for a cluster randomised control trial
AUTHORS	Sharma, Sita; Alexander, Kimberly; Green, Theresa; Wu, Min-Lin (Winnie); Bonner, Ann

VERSION 1 – REVIEW

REVIEWER	Chatrenet, Antoine Centre Hospitalier Le Mans, Nephrology
REVIEW RETURNED	26-Sep-2021

GENERAL COMMENTS	The study protocol entitled “Energy Conservation Education Intervention for People with End-stage Kidney Disease Receiving Haemodialysis (EVEREST): protocol for a cluster randomised control trial” is well designed and practical aspects such as the blinding process are feasible with the limitation inherent to the dialysis unit. Thus, this study protocol is acceptable, however, several points as listed below need to be clarified. - The definition of Chronic Kidney Disease (CKD) needs clarification. - Page 5, line 8, the citation which explain that higher level of fatigue increase mortality rate is not Picariello (2016), but Bossola (2015) as cited by themselves. - Page 5, line 29; sorry but the sentence “exercise may not be safe for all people” disturbed me, because all patients, with its own capacities (and with a professional management) can perform safe physical activities, in my opinion. In addition, the citation used to support this sentence did not report any aspect of this idea. Please clarify. - Page 6; in my opinion, the use of “EVEREST” in order to explain the educational approach of your study is not appropriate because EVEREST is the name of the trial where you will use educational approach. For example, controls will not receive educational management but they still in the EVEREST trial. - It is probably due to the fact that I’m not an expert of the sample size calculation but I’m not able to reproduce it despite that I used G*Power and the intra-cluster coefficient adjustment with the equation provided in Killip S. et al., 2004 (PMID: 15209195). For the sake of reproducibility, it is preferable if you can add reference or details about attrition adjustment. - Kt/v calculation can be an interesting additional measurement - I suggest to take advantage of the generalized linear model in order to control clinical data such as anemia, Kt/v or other variable which could be involved in the fatigue symptom. - The date of the start of the study is awaited as it is asked in the BMJ Open authors guidelines for the study protocol.

	Formatting points: - “If eGFR <15” should be reworded. - Page 4, line 34; delete “is” - CGA should be defined despite that it is commonly used. - Please reword the 2nd sentence of the Sample size section. - In the discussion section, define KRT at the first use, or delete the abbreviation if you don’t use it after.

REVIEWER	Finderup, Jeanette Aarhus Universitetshospital, Renal Medicine
REVIEW RETURNED	11-Nov-2021

GENERAL COMMENTS	Thank you for conducting this very important trial testing the effectiveness of an energy conversation intervention among patient on haemodialysis also that you have chosen to publish your protocol. The paper gives a very clear description of your project. Some comments for improvements: • You use the term 'renal'. International guidelines recommend to avoid this term and use e.g. the term 'kidney' instead. • You use some abbreviation without introduction e.g. KRT and ESKD. Some you could avoid as an abbreviation. • You have chosen to give the control group only the booklet afterwards and not the entire intervention, but do not explain why. Is the booklet to be used without the face-to-face meeting? • You name the IPOS-renal wrong; it is 'the integrated palliative outcome scale'. I would like a comment about using a palliative outcome scale. The POS-organisation recommend a specific translation and cultural adaptation process, which you have not chosen to use. I would like a comment about that. • In your randomisation process, I would like that you take day shift and night shift into account because it may impact your primary outcome. I were not able to identify clinical data such anaemia data in your patient characteristic, which I also think will impact your outcome. • I do not find any information when you plan to start and end your trial.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Antoine Chatrenet, Centre Hospitalier Le Mans

Comment: The definition of Chronic Kidney Disease (CKD) needs clarification.
Response: Thank you for this comment. The paragraph is revised (page 4).

Comment: Page 5, line 8, the citation which explain that higher level of fatigue increase mortality rate is not Picariello (2016), but Bossola (2015) as cited by themselves.
Response: Amended

Comment: age 5, line 29; sorry but the sentence “exercise may not be safe for all people” disturbed me, because all patients, with its own capacities (and with a professional management) can perform

safe physical activities, in my opinion. In addition, the citation used to support this sentence did not report any aspect of this idea. Please clarify.
Response: Thank you for this comment. We have modified this sentence as “however barriers such as having sufficient available expert staff, dialysis-related fatigue, comorbid conditions, and lack of motivation may limit the ability for some to be actively involved in exercise” (Jhamb et al., 2016)

Comment: Page 6; in my opinion, the use of “EVEREST” in order to explain the educational approach of your study is not appropriate because EVEREST is the name of the trial where you will use educational approach. For example, controls will not receive educational management but they still in the EVEREST trial.
Response: Thank you for this comment and the manuscript has been amended.

Comment: It is probably due to the fact that I’m not an expert of the sample size calculation but I’m not able to reproduce it despite that I used G*Power and the intra-cluster coefficient adjustment with the equation provided in Killip S. et al., 2004 (PMID: 15209195). For the sake of reproducibility, it is preferable if you can add reference or details about attrition adjustment.
Response: Thank you for this comment. Below is how we calculated sample size using G*power.
Test Family: t tests
Statistical tests: means difference between two independent means (two groups).
Type of power analysis: A priori: compute required sample size given α, power and effect size
Input parameters
Tails: Two, Effect size d: 0.8, α error prob: 0.05, Power (1-βerror prob): 0.80, Allocation ratio N2/N1: 1
It gives a sample size of 52.

Further, a moderate intra-cluster coefficient (ICC) of 0.03 and cluster size of 26 participants is used to inflate calculation. The calculation is further increased by 20 % to consider the attrition and again by 15% to avoid the possibility of non-normality of data that force for non-parametric statistics.

The formula for calculating the design effect (DE) = 1 + p (m - 1)
Where m = number of participants in a cluster, p = intra-cluster correlation coefficient (ICC)
DE = 1+ 0.03× (26 - 1) = 1.75
Then sample adjusting for clustering
Required sample size = effective sample size × design effect
= 26×1.75 = 45.5
Further sample size is adjusted for 20 % attrition = 45.5+45.5×20%=54.6
Final sample size after accounting for 15% possibility of non-parametric statistic= 54.6 + 54.6 ×15%=62.79=63 per group×2=126

Comment: Kt/v calculation can be an interesting additional measurement
Response: Thank you for the comment. As Nepal is a low-income country where patients have to pay for all laboratory tests, it is not possible to gather this data.

Comment: I suggest to take advantage of the generalized linear model in order to control clinical data such as anemia, Kt/v or other variable which could be involved in the fatigue symptom.
Response: Thank you for the comment. We have chosen to use Linear Mixed Model (LMM) over generalised linear model mainly because this statistical test deals with missing data according to intention to treat analysis. With this model when data are missing for one point, data doesn’t need to be imputed or to be deleted like in GLM (Field, 2013). With LMM also we can control for variables such as anaemia which may affect results.

Comment: The date of the start of the study is awaited as it is asked in the BMJ Open authors guidelines for the study protocol.

Response: Study start date: April 2021, Anticipated end date: February 2022.

Formatting points
Comment: If eGFR <15" should be reworded.
Response: Amended

Comment: Page 4, line 34; delete "is"
Response: Amended

Comment: CGA should be defined despite that it is commonly used.
Response: The paragraph is modified.

Comment: Please reword the 2nd sentence of the Sample size section.
Response: Thank you for the comment. Amended

Comment: In the discussion section, define KRT at the first use, or delete the abbreviation if you don't use it after.
Response: Amended

Reviewer: 2
Dr. Jeanette Finderup, Aarhus Universitetshospital

Comment: You use the term 'renal'. International guidelines recommend to avoid this term and use e.g. the term 'kidney' instead.
Response: Amended throughout the manuscript

Comment: You use some abbreviation without introduction e.g. KRT and ESKD. Some you could avoid as an abbreviation.
Response: Amended

Comment: You have chosen to give the control group only the booklet afterwards and not the entire intervention, but do not explain why. Is the booklet to be used without the face-to-face meeting?
Response: The reasons we have chosen to give the control group only the booklet and not the entire intervention are due to limitations of time and budget for this study. We are unable to train the staff working in the centre at this time.

Comment: You name the IPOS-renal wrong; it is 'the integrated palliative outcome scale'. I would like a comment about using a palliative outcome scale. The POS-organisation recommend a specific translation and cultural adaptation process, which you have not chosen to use. I would like a comment about that.
Response: The full form of IPOS-renal is amended. Added to other kidney symptom subsection is the following:
The IPOS-renal is designed to be used in chronic kidney disease populations including those receiving HD. This self-report instrument is short (11-items) making it quick and easy to administer. It measures the most common symptoms experienced by people with kidney disease; additional items such as information needs, practice issues; and anxiety of family (page no.13).
Due to time limitations, we used a translation, cultural adaptation, and validation process internationally used to translate instruments from one language into another language (Sousa & Rojjanasrirat, 2011). Most of the steps used in this process are the same as those recommended by the POS organisation. As this study is conducted in a low-income country, and the IPOS-renal is used to measure secondary outcomes, we were unable to undertake further translation steps.

Comment: In your randomisation process, I would like that you take day shift and night shift into account because it may impact your primary outcome. I were not able to identify clinical data such anaemia data in your patient characteristic, which I also think will impact your outcome.
Response: Thank you for this comment.
There is no night shift at this haemodialysis centre. In addition, patients on morning or afternoon shifts are swapped due to clinical need however, they tend not to change days.
The Following sentence is already included in the randomisation subsection (page 16)
“Instances of participants attending different dialysis shifts and being potentially exposed to the intervention will be documented.”
On page 15, we identify clinical data collected including haemoglobin level at different time points.

Comment: I do not find any information when you plan to start and end your trial.
Response: Study start date: April 2021, Anticipated completion date: February 2022 added to method section.