PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The EX-FRAIL CKD Trial: a study protocol for a pilot randomised controlled trial of a home-based EXercise programme for pre-FRAIL and FRAIL, older adults with Chronic Kidney Disease
AUTHORS	Nixon, Andrew; Bampouras, Theodoros; Gooch, Helen; Young, Hannah; Finlayson, Kenneth; Pendleton, Neil; Mitra, Sandip; Brady, Mark; Dhaygude, Ajay

VERSION 1 - REVIEW

REVIEWER	Yugo Shibagaki St. Marianna University, Japan
REVIEW RETURNED	29-Nov-2019

GENERAL COMMENTS	Nixon et al. submitted a study protocol for the RCT of home-based exercise program for pre-frail or frail patients with CKD. Since studies to examine the efficacy and the effectiveness of exercise in patients with non-dialysis dependent CKD are very scarce, and since the home-based exercise is much more practical and can be adopted for more patients than monitored exercise program, the planned study are very important and deserve attention. The design of the study is very well structured. There are still several comments to this protocol. 1) In the previous study by Hiraki et al. (BMC Nephrol. 2017 Jun 17;18(1):198.), they also explored the effectiveness of home-base exercise program in non-dialysis dependent CKD population and proved the feasibility of home-based exercise program. They tried to check the objectiveness of participants' physical activity by using the pedometer. In your study, how you can assure the objectiveness of the enhanced physical activity by exercise guidance. It is very important to guarantee the actual increase in physical activity if we show the effectiveness of "home-base" or non-monitored exercise program. 2) I have a concern that the degree of the exercise load is relatively mild which may not be so effective to promote physical function. Why the authors dare to select this mild exercise? Is this because the main objective of the study is feasibility of the home-based program? 3) The study also needs to guarantee the appropriate participants' cognitive function to complete the program. Since "home-based" exercise needs high self-management ability to complete the program, especially if authors set feasibility as primary outcome.

REVIEWER	K Kamiya Department of Rehabilitation, School of Allied Health Sciences, Kitasato University
REVIEW RETURNED	17-Dec-2019

GENERAL COMMENTS	In the manuscript titled “The EX-FRAIL CKD Trial: A Study Protocol for a Pilot Mixed-Methods Randomised Controlled Trial of a home-based EXercise programme for pre-FRAIL and FRAIL, older adults with Chronic Kidney Disease”, Nixon and colleagues presented the rationale and the protocol of multicenter study investigating the effectiveness of hoome-based exericise for frail or pre-frail elderly CKD patients. The manuscript presents clear rationale and design. I have the following comments: -Page 12, Timeline: By whom and at what stage will the CFS assessment be performed? Will this be evaluated by the question method over the phone as described in the paragraph on the “Timeline" in the methods section? If CFS evaluation is performed by question method using a telephone, has the reliability and validity been verified? (Reference is required) -Figure 1, “Screened Prior to Eligibility Assessment” : What kind of evaluation is used for this screening and by whom and for which patient will it be performed on? Will the evaluation sheet be handed to all elderly patients with CKD stage 3-5b? Please state clearly.

REVIEWER	Joy Adamson University of York
REVIEW RETURNED	05-Feb-2020

GENERAL COMMENTS	There were some points of clarification: - wasn't keen on calling the study 'pilot mixed methods RCT', felt a bit odd, maybe pilot RCT with nested qualitative interview study? - I couldn't see the dates of the study? - is it efficacy or effectiveness? - in the summary of strengths/limitations, it wasn't clear how using the validated frailty assessment would strengthen the conclusions, in what way? - exclusion criteria mis-numbered - need some clarity on the order of events at start of trial, wasn't sure about enrolling people in the study and then withdrawn if they do not meet exclusion criteria; when are the baseline outcome measures to be taken, it implied this was post-randomisation? I would expect this to be that participants would be enrolled into the study if they fulfil the eligibility criteria and provide written consent to take part in the study, then they would be randomised to either the intervention or control arm AFTER they have completed the baseline outcome measures? - is there a logic model for the intervention? - how will adherence to the intervention be measured? - how will qual and quant findings be 'linked'? For discussion: - could mention that whilst they had put in place measures to enhance fidelity, this wasn't being formally assessed in the pilot

	- health economics missing - could have planned to interview those who refused to participate in the study

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1) In the previous study by Hiraki et al. (BMC Nephrol. 2017 Jun 17;18(1):198.), they also explored the effectiveness of home-base exercise program in non-dialysis dependent CKD population and proved the feasibility of home-based exercise program. They tried to check the objectiveness of participants' physical activity by using the pedometer. In your study, how you can assure the objectiveness of the enhanced physical activity by exercise guidance. It is very important to guarantee the actual increase in physical activity if we show the effectiveness of "home-base" or non-monitored exercise program.

Response: Physical activity levels may well increase because of participation in the exercise programme due to associated improvements in mobility, strength and balance. However, physical activity itself is not one of our outcomes of interest, rather the consequences of involvement in the exercise programme (and any associated increase in physical activity levels), i.e. physical function, health-related quality of life, etc. In this context, we believe that it is more important to focus on adherence to the programme (using the exercise diaries and information obtained during weekly telephone calls) to evaluate if home-based exercise is viable.

2) I have a concern that the degree of the exercise load is relatively mild which may not be so effective to promote physical function. Why the authors dare to select this mild exercise? Is this because the main objective of the study is feasibility of the home-based program?

Response: We anticipate that patients recruited to the study will most likely be deconditioned and likely not used to regular physical activity. We therefore reasoned that introducing the exercises gradually would be safer and minimise the risk of participant drop out. This approach reflects exercise prescription in clinical practice. The American College of Sports Medicine and American Heart Association Guidelines highlight the importance of physical activity being increased gradually in older adults, particularly those that are very deconditioned [1]. This was further supported by the recent position statement from the National Strength and Conditioning Association on resistance training for older adults: “to optimize functional capacity, resistance training programs should include familiarization to training in which the subjects' body mass is used for resistance and in which usual daily activities are simulated (such as the “sit-to-stand” exercise)” [2]. The American College of Sports Medicine and American Heart Association Guidelines also recommend that older adults who reduce their sedentary behaviour, even if not to the level recommended, still attain health benefits [1]. We hypothesise that older adults living with frailty and CKD who increase physical activity levels, even modestly, may have associated health benefits, including improved health-related quality of life. We would add that we use the Borg Rating of Perceived Exertion Scale to ensure that a moderate intensity is achieved for exercises 2-6. We acknowledge that modification of the exercise programme may be required based on the findings of our pilot study.

3) The study also needs to guarantee the appropriate participants' cognitive function to complete the program. Since "home-based" exercise needs high self-management ability to complete the program, especially if authors set feasibility as primary outcome.

Response: Patients must also be able to give informed consent to be eligible for study enrolment, therefore patients with cognitive impairment that is severe enough to impact their capacity to decide to

become involved in the study will not be enrolled. Furthermore, an exclusion criterion is ‘clinical and/or research team consider participation in the exercise programme unsafe’. Patients are assessed by a clinician and physiotherapist at the initial visit and weekly thereafter during telephone calls. If there are any concerns that an individual is unable to complete the exercise programme safely due to cognitive impairment or any other cause, they will not be enrolled in the study (or if enrolled in the study, they will be withdrawn). We did not want to include cognitive impairment as an exclusion criterion as there is a high prevalence of mild cognitive impairment in this patient population. We hypothesise that exercise will have benefits for those living with mild cognitive impairment and frailty, provided that the individual is appropriately supported by the research team and family members. We therefore considered it unethical to exclude patients with mild cognitive impairment. Of course, the pilot study findings may suggest that a modification to a definitive randomised controlled trial is needed if it is apparent that cognitive impairment is affecting exercise adherence.

Reviewer 2
Page 12, Timeline: By whom and at what stage will the CFS assessment be performed? Will this be evaluated by the question method over the phone as described in the paragraph on the “Timeline" in the methods section? If CFS evaluation is performed by question method using a telephone, has the reliability and validity been verified? (Reference is required)

Response: The Clinical Frailty Scale is frailty screening measure used within usual care and is therefore not a study specific measure. The rationale for using this screening measure within the inclusion criteria was to minimise the number of robust individuals approached for study consent. Consented individuals then have a formal frailty assessment using the Frailty Phenotype. Only participants categorised as pre-frail or frail by the Frailty Phenotype undergo randomisation. The Clinical Frailty Scale is used in our trust in outpatient clinics by clinicians and clinical nurse specialists. We have revised the ‘Inclusion Criteria’ section to make this clearer.

Figure 1, “Screened Prior to Eligibility Assessment”: What kind of evaluation is used for this screening and by whom and for which patient will it be performed on? Will the evaluation sheet be handed to all elderly patients with CKD stage 3-5b? Please state clearly.

Response: Patients will be screened by members of the clinical team (based on age, CKD stage and Clinical Frailty Scale score). Patients aged 65 years or above with CKD G3b-5 and a Clinical Frailty Scale score 4 or above will be given a participant information sheet. We have now detailed this in the ‘Timeline’ section.

Reviewer 3
There were some points of clarification:

Wasn't keen on calling the study 'pilot mixed methods RCT', felt a bit odd, maybe pilot RCT with nested qualitative interview study?

Response: We have changed the study title as recommended.

I couldn't see the dates of the study?

Response: We have now added study dates to a final section titled ‘Trial status’: “The study opened in August 2018 and the first participant was recruited in November 2018. Data collection was completed in December 2019”. The manuscript was submitted in October 2019.

Is it efficacy or effectiveness?

Response: Thank you for highlighting this. It is ‘effectiveness’ except in the case of the Falls Efficacy Scale-International Tool. We have amended the manuscript accordingly.

In the summary of strengths/limitations, it wasn't clear how using the validated frailty assessment would strengthen the conclusions, in what way?

Response: We have included the following paragraphs within the timeline section, which we hope makes our statement clearer: Our previous study demonstrated that a Clinical Frailty Scale score of 4 or above had a sensitivity and specificity for identifying frailty of 1.00 and 0.55, respectively [3]. Given the risk of false positives, we considered it prudent to perform a more objective frailty assessment to ensure that only patients with pre-frailty or frailty underwent randomisation.

Exclusion criteria mis-numbered

Response: Thank you for highlighting this. We have made the correction.

Need some clarity on the order of events at start of trial, wasn't sure about enrolling people in the study and then withdrawn if they do not meet exclusion criteria; when are the baseline outcome measures to be taken, it implied this was post-randomisation? I would expect this to be that participants would be enrolled into the study if they fulfil the eligibility criteria and provide written consent to take part in the study, then they would be randomised to either the intervention or control arm AFTER they have completed the baseline outcome measures?

Response: As described above, the Clinical Frailty Scale is a screening tool used to identify individuals at risk of frailty. Our previous study demonstrated that a Clinical Frailty Scale score of 4 or above had a sensitivity and specificity for identifying frailty of 1.00 and 0.55, respectively [3]. Given the risk of false positives, we considered it prudent to perform a more objective frailty assessment using the accepted standard, the Frailty Phenotype. The Frailty Phenotype assessment is not a routine assessment in clinical care, therefore it cannot be performed unless patients consent to study involvement. We therefore perform the Frailty Phenotype assessment following participant consent. Participants are withdrawn at this point if they are not categorised as pre-frail or frail. This possible eventuality is explained to patients prior to study consent. Participants that were categorised as pre-frail and frail then undergo the remaining baseline assessments followed by randomisation. We hope the changes to the ‘Timeline’ section describe this more clearly.

Is there a logic model for the intervention?

Response: We have now included an additional figure detailing the logic model.

How will adherence to the intervention be measured?

Response: Adherence will be assessed by telephoning participants weekly to review the preceding week’s exercise activity and by reviewing participant exercise diaries at the end of the study period. This is described in the ‘Primary Feasibility Outcome Measures’ section.

How will qual and quant findings be 'linked'?

Response: We have updated the analysis plan to include the following: Qualitative and quantitative findings will be linked using a triangulation approach as described by Farmer et al [4] to provide a more comprehensive understanding of trial and intervention acceptability.

For discussion:

Could mention that whilst they had put in place measures to enhance fidelity, this wasn't being formally assessed in the pilot

Response: All exercise education sessions are delivered by the same physiotherapist, who aimed to maintain a consistent approach. Although the education sessions are not formally observed, there are other assessments of intervention fidelity:
1. Participant ability to perform specific exercises is assessed during educational sessions.
2. Participants ability to engage in self-monitoring (using the exercise diary) is assessed.
3. Telephone pro forma are reviewed to check that the same predetermined topics are discussed during each telephone call.
4. Participant experience of the exercise education sessions and exercise progression is explored in the qualitative interviews.

Health economics missing

Response: It is not the intention of the EX-FRAIL CKD trial to assess health economics, though this may be considered in a definitive randomised controlled trial.

Could have planned to interview those who refused to participate in the study.

Response: We acknowledge that this is a limitation. We have now included the following in the 'Discussion' section: For pragmatic reasons, patients that decline to participate in the study will not be invited to participate in an interview. However, participants that decide to stop exercising earlier than planned will be invited to participate in an interview to explore their experience of the study. Furthermore, participants' rationale and motivation for enrolling in the study will be explored during interviews.

VERSION 2 – REVIEW

REVIEWER	Yugo Shibagaki St Marianna University, JAPAN
REVIEW RETURNED	06-Mar-2020

GENERAL COMMENTS	The concerns I have raised in the previous review, were almost answered appropriately. I have no further comments or concerns in publishing this article.

REVIEWER	Joy Adamson University of York, UK
REVIEW RETURNED	10-Mar-2020

GENERAL COMMENTS	I think the paper is much improved and the authors have addressed the comments well.