PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	'Self-Management Intervention through Lifestyle Education for Kidney health' (the SMILE-K study): protocol for a single-blind longitudinal randomised control trial with nested pilot study
AUTHORS	Lightfoot, Courtney; Wilkinson, Thomas; Yates, Thomas; Davies, Melanie; Smith, Alice

VERSION 1 – REVIEW

REVIEWER	Lunardi , Laura E.
REVIEW RETURNED	06-Aug-2022

GENERAL COMMENTS	Interesting study. Looking forward to seeing the results of this study

REVIEWER	Murea, Mariana Wake Forest Baptist Medical Center
REVIEW RETURNED	15-Aug-2022

GENERAL COMMENTS	Lightfoot and Wilkinson et al. present the protocol of a nested pilot study with intention to be followed by a single-blind longitudinal randomized control trial of an electronic patient education and self-management program called 'My Kidneys & Me'. Major comments 1. Clarify the primary outcome for the pilot study and for the full RCT. I suspect the primary outcome for the initial pilot study is feasibility; and for the full RCT is PAM-13 score. This does not come across clearly in the abstract and in the main text. 2. Progression, 'stop/go' criteria from pilot study to full RCT is a core piece of the protocol yet it seems to not have been finalized. This Reviewer believes that these criteria need to be finalized and presented with the publication of the study protocol. 3. Clarify who is blinded to the intervention 4. More information is needed on how the statistical analysis of the primary outcome of PAM-13 in the full RCT. This should be based on potential differences in variables known to impact outcomes that may be seen longitudinally. For example, patients in the intervention group may have better adherence to outpatient follow-up with their providers; this, in turn, can influence PAM-13, medication adherence and other clinical outcomes, independent of the 'My Kidneys & Me' program. Consider acknowledging this limitation and discussing how these data will be collected and addressed statistically. 5. Table 1: - at the beginning of the table, consider inserting a few rows that give a brief description of the Learning Sessions - for all the rows, consider adding column that indicates the (estimated or actual, depending on the case) length of each video

	material (for both Learning Sessions and Booster Sessions) 6. Table 2 legend indicates “Qualitative interviews may be performed at any of the time points”. This Reviewer believes the schedule of interviews should be standardized across participants. 7. There seems to be a significant amount of surveys and evaluations in a relatively short time span. This carries a risk of overburdening the participants and affecting missing data and evaluation accuracy. This should either be acknowledged as a limitation or reassessed as to whether the number of evaluations at each visit can be abridged. 8. Clarify sub-study assessments. Page 15, lines 51-52: “In an optional sub-study, the following additional physical assessments will be performed during a visit to a hospital site”. Are the assessments done at the same time/day with the main study assessments? 9. The reliance on the patients to perform STS is unusual and seems to be a limitation. Page 16, lines 54-55 “The STS-60 test involves completing as many STS cycles as possible in 60 seconds. Participants will also be asked to record a STS-60 score as part of the online survey.” What is the sensitivity and accuracy of such an approach? Has this been studied before? Will the participants need to be supervised when doing this test? 10. More information is needed on Sample Size Calculation. What statistical power at two-sided alpha will n=432 (2:1) provide to detect 4 point MID? What is the expected attrition rate? Minor comments 1. Abstract Methods and Analysis: consider revising the sentence: Consider clarifying what the intervention is after the sentence “Participants will be randomized into two groups: intervention group and control group”. Perhaps move some parts of the Abstract Introduction after the mentioned sentence and clarify if the intervention is added to usual care; and if control group is just usual care. 2. Note word duplicate ‘exploring’ on page 18, line 24 3. Clarify the sentence “regardless of their actual compliance with treatment” on page 19, line 18. I suspect ‘treatment’ is the digital intervention. Also clarify what you will qualify as low/poor adherence to intervention and how the analysis on the relationship of % adherence and PAM-13 will be addressed statistically.

REVIEWER	Nowicki, Michal Med Univ Lodz, Nephrology
REVIEW RETURNED	22-Aug-2022

GENERAL COMMENTS	The study rationale, methods and protocol are described in details and reads very well. My only comment refers to blinding. The authors should describe the potential problems related to a single blinding that may be difficult for this type of the study. I would appreciate if the authors provided information or a table listing the potential strengths and limitations of the planned study.

VERSION 1 – AUTHOR RESPONSE

Reviewer 2 comments

Comment Clarify the primary outcome for the pilot study and for the full RCT. I suspect the primary outcome for the initial pilot study is feasibility; and for the full RCT is PAM-13 score. This does not

come across clearly in the abstract and in the main text.

Response Yes, the primary outcome for the initial pilot study is feasibility, and the full RCT is PAM-13 score. We have amended the abstract and main text to read:
"The primary outcome of the nested pilot study is feasibility and the primary outcome of the full RCT is the Patient Activation Measure (PAM-13)"

Change Abstract, page 2
Main text, pages 10 and 11

Comment Progression, 'stop/go' criteria from pilot study to full RCT is a core piece of the protocol yet it seems to not have been finalized. This Reviewer believes that these criteria need to be finalized and presented with the publication of the study protocol.

Response The progression criteria for the pilot study to the full RCT has now been pre-specified and finalised. The process involved the co-production of the progression criteria which was conducted in two stages and comprised clinicians and researchers. We plan to include the full development process for the progression criteria in detail in a subsequent feasibility manuscript of the pilot study. As such, we feel that the inclusion of the process conducted to develop the progression criteria within the protocol paper here would dilute the work involved.

Change No change

Comment Clarify who is blinded to the intervention
Response Study investigators, clinicians, and research staff from external recruiting sites are blinded as to which participants receive the intervention. We have detailed this in the randomisation section of the manuscript.

Change Page 7, paragraph 3

Comment More information is needed on how the statistical analysis of the primary outcome of PAM-13 in the full RCT. This should be based on potential differences in variables known to impact outcomes that may be seen longitudinally. For example, patients in the intervention group may have better adherence to outpatient follow-up with their providers; this, in turn, can influence PAM-13, medication adherence and other clinical outcomes, independent of the 'My Kidneys & Me' program. Consider acknowledging this limitation and discussing how these data will be collected and addressed statistically.

Response Thank you for your suggestion. The initial power calculation was conducted based on current data available. Whilst PAM-13 has been validated for people with CKD, the minimal clinically significant difference (MCID) of PAM-13 in CKD is unknown. Following the pilot study, we aim to recalculate the sample size using the effect sizes obtained from the pilot data. This will be detailed in the feasibility. We acknowledge this in the new considerations session within the manuscript, and aim to identify the MCID with data from the full RCT.

It may be that patients in the intervention group "have better adherence to outpatient follow-up with their providers"; however, we hope this is mitigated by the inclusion of randomised control group in the study. It is likely that patients in the intervention group will have better adherence to outpatient follow-up with their providers given that 'My Kidneys & Me' programme contains educational sessions about healthcare team involvement, healthcare appointments, medications, alongside the 'how to' sessions which encourage people to make behavioural changes and get the most from their healthcare. We see this as a positive effect of the programme. This will be evaluated as part of the full RCT as we are interested in the relationship between patient activation and health-related behaviours.

As specified in the manuscript, analysis will be performed using 'intention-to-treat' (ITT) analysis to provide a pragmatic insight into whether the programme is effective. ITT analysis avoids overestimating any efficacy of an intervention resulting from the removal of non-compliers (or e.g.,

patients better adherence) by accepting that non-compliance and protocol deviations are likely to occur in actual clinical practice.
Change Page 19, paragraph 2

Comment Table 1:
- at the beginning of the table, consider inserting a few rows that give a brief description of the Learning Sessions
- for all the rows, consider adding column that indicates the (estimated or actual, depending on the case) length of each video material (for both Learning Sessions and Booster Sessions)

Response Thank you for your suggestion. A summary of the learning sessions is available in the manuscript detailing the development of My Kidneys & Me, which is fully referenced throughout the current manuscript. We do not feel that it is necessary to also include them in the protocol paper, given their description may be excessive. However, we noted that the educational sessions can be found elsewhere:
"A summary of the education sessions can be in the My Kidneys & Me development paper23."

Change Page 8, paragraph 2

Comment Table 2 legend indicates "Qualitative interviews may be performed at any of the time points". This Reviewer believes the schedule of interviews should be standardized across participants.

Response Up to three interviews will be conducted with participants depending on their voluntary participation and/or their status in the study. Participants may be interviewed pre- and/or post-intervention (at 10-weeks), and/or after the follow up phase (at 20-weeks). Whilst we ideally would interview participants at all three time points, this may not be feasible and can increase the burden to the participants. We have added this information to the manuscript.

Change Page 16, paragraph 5

Comment There seems to be a significant amount of surveys and evaluations in a relatively short time span. This carries a risk of overburdening the participants and affecting missing data and evaluation accuracy. This should either be acknowledged as a limitation or reassessed as to whether the number of evaluations at each visit can be abridged.

Response Whilst we acknowledge that a large amount of surveys and assessments can potentially overburden participants, we received input from our patient steering group regarding the acceptability of the questionnaires. The majority of surveys are short in duration, and relatively easy to fill in. This is already detailed in our patient and public involvement section, we have had input from our patient steering group regarding the surveys:
"The patient steering group assisted with the selection of questionnaires for the study, and reviewed the final questionnaire survey to ensure that it was acceptable."

The surveys are conducted online, and the participant can complete them at their own leisure. There is the option for them to save their progress and return to the survey at a later date. The sub-study which involves addition physical assessments and/ or semi-structured interviews is optional to participants. If a participant opts to take part in the physical assessments and an interview, these can be conducted in a single visit or multiple visits depending on the participant's preference. The interviews can also be conducted via telephone if the participant does not want to or is unable to attend a face-to-face interview. This is detailed in the outcomes section.

Indeed, the feasibility component of the study will assess outcome measure completion, particularly around our proposed primary outcome (PAM-13). We will make necessary adjustment and changes if the feasibility data suggests that outcome measures are not being completed.

Change No change

Comment Clarify sub-study assessments. Page 15, lines 51-52: “In an optional sub-study, the following additional physical assessments will be performed during a visit to a hospital site”. Are the assessments done at the same time/day with the main study assessments?

Response The main study assessments are conducted using an online survey platform and will be completed by the participant at their own leisure. The sub-study physical assessments will be completed during a visit to the hospital. Study visits will be kept to a minimum for the sub-study. These will be arranged at the convenience of the participant. All out-of-pocket expenses (i.e. travel mileage/public transport, parking) will be reimbursed on the day

We have added the follow:
“The main study assessments will be conducted online using Jisc Online Surveys (University of Leicester)”

“In an optional sub-study, the following additional physical assessments will be performed during a visit to a hospital site at a time that is convenient for the participant”

Change Page 11, paragraph 1
Page 15, paragraph 2

Comment The reliance on the patients to perform STS is unusual and seems to be a limitation. Page 16, lines 54-55 “The STS-60 test involves completing as many STS cycles as possible in 60 seconds. Participants will also be asked to record a STS-60 score as part of the online survey.” What is the sensitivity and accuracy of such an approach? Has this been studied before? Will the participants need to be supervised when doing this test?

Response Thank you for your comment. The notion of conducting a remote STS was required due to the remote delivery of the study (and partly confounded by restrictions around COVID-19 during study conception and early delivery). At the time of protocol development, there had been limited experience on the conduction of remote physical function testing. Current literature suggests that such tests can be supervised remotely via video conferencing software, and evidence shows assessing functional capacities and muscle function remotely is as reliable and valid as a face-to-face assessment and should be considered as a clinical practice (e.g., Peyrusque et al. 2022). Nonetheless, these still require remote supervision, which, given the pragmatic nature and scale of our study and the number of participants to be recruited, we felt was not feasible or cost and time effective.

We acknowledge there may be limitations in asking participants to perform an ‘unsupervised’ test and we are unaware of any primary research comparing the relatively and validity of the conduction of supervised vs unsupervised physical function testing. We do have some small preliminary data from the pilot component of this study which suggests that the ~mean values in the current study are similar to that reported in our previous research in a similar participant population (approximately matched for age, sex, CKD stage, and self-reported function using the SF-12 physical function domain). We will ensure the limitations in this are acknowledged in subsequent papers, but believe its inclusion strikes the correct balance of being pragmatic in the current design.

Participants will be given minimal guidance via an instruction sheet, but no other instructions (i.e. monitoring via a video call). We have added the following:
“Minimal guidance via an instruction sheet will be provided for participants, but no other instructions (i.e. monitoring via a video call) will be utilised”

Change Page 16, paragraph 1

Comment More information is needed on Sample Size Calculation. What statistical power at two-sided alpha will n=432 (2:1) provide to detect 4 point MID? What is the expected attrition rate?

Response The required power to detect a minimal clinically significant difference of 4 points in the PAM-13 was 0.8. The expected attrition rate is 25%.

We have included the following:
“This was based on previously published PAM-13 data by our group13 and on the required power (β=0.8; α=0.05) to detect a minimal clinically significant difference of 4 points in the PAM-1345-47, and an expect attrition rate of 25%”

Change Page 18, paragraph 1

Comment Abstract Methods and Analysis: consider revising the sentence: Consider clarifying what the intervention is after the sentence “Participants will be randomized into two groups: intervention group and control group”. Perhaps move some parts of the Abstract Introduction after the mentioned sentence and clarify if the intervention is added to usual care; and if control group is just usual care.

Response The intervention is our evidence- and theory-based digital self-management structured 10-week programme developed for CKD patients called ‘My Kidneys & Me’. We have amended the sentence to read:
“Participants will be randomised into two groups: intervention group (receive My Kidneys & Me in addition to usual care) and control group (usual care)”

Change Page 2 (Abstract), paragraph 2

Comment Note word duplicate ‘exploring’ on page 18, line 24
Response Thank you. We have now removed the duplicate
Change Page 17

Comment Clarify the sentence “regardless of their actual compliance with treatment” on page 19, line 18. I suspect ‘treatment’ is the digital intervention. Also clarify what you will qualify as low/poor adherence to intervention and how the analysis on the relationship of % adherence and PAM-13 will be addressed statistically.

Response Yes, this relates to their compliance with the intervention. We have now included the word intervention in the sentence.

There is limited evidence available about what classes as low or poor adherence to a digital intervention such as ours. This is the first intervention of its kind, to our knowledge, and thus it is unknown how people with CKD may engage with an online educational self-management programme. My Kidneys & Me has been designed to be flexible and for patients to use it as they wish, so there may be some topics that are not relevant and so may not complete them. As part of this study, we will evaluate programme usage and adherence to My Kidneys & Me, and patient experiences of the programme. These findings will help us understand how the programme is being used. Thus, we are reluctant to pre-define what we would consider to be low adherence.

Change Page 18, paragraph 2

Reviewer 3 comments

Comment The study rationale, methods and protocol are described in details and reads very well. My only comment refers to blinding. The authors should describe the potential problems related to a single blinding that may be difficult for this type of the study. I would appreciate if the authors provided information or a table listing the potential strengths and limitations of the planned study.

Response Thank you for your comment. We are glad to hear that we have described our study rationale, methods and protocol in detail and that our manuscript reads well.

As described above in response to Reviewer 2, study investigators, clinicians, and research staff from external recruiting sites are blinded as to which participants receive the intervention. We have detailed this in the randomisation section of the manuscript.

Change Page 7, paragraph 3

VERSION 2 – REVIEW

REVIEWER	Murea, Mariana Wake Forest Baptist Medical Center
REVIEW RETURNED	16-Sep-2022

GENERAL COMMENTS	The authors have addressed my suggestions. I have no further comments.