Author’s response to reviews

Title: INfluence of Successful Periodontal Intervention in Renal Disease (INSPIRED): study protocol for a randomised controlled pilot clinical trial.

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Author’s response to reviews:

We thank the editor and reviewers for taking the time to review this manuscript. The changes suggested were very relevant and implementing them has improved the manuscript. Please find below the point-by-point breakdown of changes made.

Reviewer reports:

Reviewer #1:

1) The CKD EPI equation was suggested to predict outcomes more accurately as compared to the MDRD equation (JAMA. 2012;307(18):1941-1951. doi:10.1001/jama.2012.3954) - why was the latter chosen over the former to classify patients into CKD stages? Would a sensitivity analyses make sense to quantify the extent to which (differential) misclassification may have affected the associations?

Thank you for the suggestion. Currently, the clinical laboratory service locally is reporting eGFR by MDRD, however we will calculate CKD-EPI eGFR and utilise for the purposes of kidney function reporting from the study. At the threshold for eGFR based entry for patients into the study, which is eGFR <30 ml/min/1.73 ml/min, there is very little difference between the MDRD equation and the CKD-EPI equation. Most of the impact of the equation is seen through the reclassification of patients with an eGFR of just below 60 ml/min. With regards to the rate of
decline of eGFR, there is no difference as the defining variable in the equation (serum creatinine) is the same. As a sensitivity analysis, we will also analyse the data using the CKD-EPI equation and have amended the manuscript to reflect this.

2) Given the positive effects of ascorbic acid on periodontal health (an effect quite accentuated in CKD5d pts) - did the authors think of these effects? Would a dietary recall or an assessment of vitamin supplements amongst studied patients be a worthwhile?

We thank the reviewer for this suggestion. We had not planned to carry out dietary recalls or assessments of vitamin supplements in this pilot study. However, in a definitive trial, we would expect confounders, including ascorbic acid, to be balanced between groups. To ensure that this is the case, we will consider storing serum samples specifically for vitamin C analysis in a future definitive study.

3) In the light of the longitudinal nature of the study and the assessments at several timepoints over the course of the 18 months study period I would suggest to perform longitudinal analyses using tool such as linear mixed effects models [potentially adjusted for baseline levels, operator/assessor, baseline GFR and other possibly relevant factors (i.e. blood pressure, HgbA1c, etc.)].

Thank you for suggesting this analysis plan which is entirely appropriate for the definitive trial to follow. However, we feel that this level of analysis is not appropriate in a pilot trial. The statistical plan put forth in the protocol is more in keeping with the pilot nature of this trial.

Reviewer #2:

Major Essential Revisions

1. Shorten the methods by removing all or most repeat information. One example, "60 patients with CKD and periodontitis will be randomised into one of two equal arms using a parallel group RCT design" shows up 6 times.

Thank you for this suggestion. The methods section has been shortened as suggested.

2. "At least 80% of patients recruited with full follow-up" would have been a good singular primary objective for any pilot trial. The term primary should probably be removed from the protocol as it encompasses all the pilot's objectives. Moreover, how does the "success criteria
for INSPIRED" and its primary aim fit with the broad primary objective and pilot objects mentioned earlier? These sections contradict each other.

Thank you. As pointed out by reviewer #3, the "success criteria for INSPIRED" section is superfluous. This section has been removed and the criteria for successful periodontal therapy included elsewhere.

3. The measurements at month 15 and 18 should be more clearly describe as post-trial follow-up for both arms.

This has been clarified by saying “Therefore, measurements at the 15 and 18 month time points represent post-treatment follow up measurements for both arms” at the end of the “Follow-up measurements” section.

4. On page 10, the authors state that the protocol is subject to change as the trial progresses. This is troublesome as the trial was not described as adaptive.

We understand the reviewer’s concerns regarding this. We felt that we needed to have flexibility in the trial protocol to allow us to adapt to changes in circumstances to maximise the potential of this pilot study to inform a definitive one. Without these changes, we would not have been successful in this objective. As an example, thus far, changes in the protocol have helped to improved recruitment and retention rates and these measures are likely to be taken forward in the design of the definitive trial to follow. For this reason, we would like to be able to adapt the protocol as circumstances dictate, all with the approval of the research ethics committee.

5. Will participants from both groups be supported similarly as it relates to anticipated compliance issues?

Yes. This point has been clarified by “Patients in either arm, following periodontal intervention, will be supported with this through reinforcement of oral hygiene instructions during treatment and follow-up visits along with maintenance periodontal therapy being provided as required” in the “Anticipated compliance issues” section.

6. The statistical analysis section contains many elements that are not related strictly to analysis. The information about reporting (e.g., CONSORT), data management (privacy, confidentiality, data storage), and aims/objectives (i.e., to inform suitability of outcome
measures, provide the data necessary for a sample size collection) do not belong in the statistical analysis section.

Thank you for this suggestion. These sections have been deleted as suggested.

7. Will you look for differences between the groups on dichotomous outcomes as well? How will report them? I'm also not sure what you mean when you say that the mean differences will determine sensitivity to change. Change in what?

This has been clarified by the sentence: “This will help determine the sensitivity of the outcome measures, such as eGFR, ACR, PWV, and measures of inflammation or oxidative stress to change” at the end of the “Outcome data” section.

8. Will CRP and IL-6 not be measured?

We intend to measure surrogate markers of inflammation (serum CRP, IL-6) and oxidative stress. This has been highlighted on page 7 of the manuscript.

Minor Essential Revisions

9. The term high-risk CKD is puzzling. It is used a few times before it is defined. It begs the question high-risk for what specifically. The term advanced (stage) or severe CKD would be better understood.

Thank you for this comment. The “high-risk” aspect has been clarified to indicate that these patients are at a greater risk of progression in CKD. We have not used the term advanced or severe CKD as this terminology is usually used to indicate patients with an eGFR of <30 ml/min. We have altered the manuscript to signpost that a proportion of patients recruited into the study will have advanced CKD.

10. The last sentence on page 7 needs references: "To date only a limited number of underpowered, non-randomised interventional studies have investigated the effect of periodontal therapy on renal function."

We apologise for this omission. The references have now been included.
11. Under inclusion criteria, criteria 4iii) should be described as non-dialysis CKD stage 4 or 5. Not all CKD patients will receive dialysis at a later point in time.

This has been changed as suggested.

12. Remove the first and second exclusion criteria as they are redundant given the inclusion criteria.

These points are now removed.

13. Add the term permuted to the description of block randomization. Also give the variable block sizes.

We thank the reviewer for this comment. The term permuted has now been added to the description of block randomisation. However, after consultation with our statisticians, we do not feel it is good practice to publish comprehensive details of randomisation schemes (e.g. block lengths) in a protocol, as recruitment into the trial is ongoing and this could lead to increased predictability of allocation. Hence the block sizes have not been disclosed. We hope this is agreeable to the reviewer.

14. Why can not the assessor of general health be blind to each patient’s treatment allocation?

The medical examiner, in writing electronic clinical notes, can visualise the patient’s last visit details. If the examiner sees that the patient was seen or not seen by a hygienist, they are immediately unblinded to treatment allocation. We feel that this should not affect the measurements at this station as these are objective measurements such as anthropomorphic measurements, PWV, BP etc.

15. In figure 2, Agree to participate, should be replaced with Agree to be approached as they have not yet consent according to the diagram. Also the last 6 months should be described similarly for both groups - they are post-trial follow-up periods for both treatment groups.

The flowchart of participants was designed with patient contribution. It starts with the patient being “Invited to participate” which is akin to the “agree to be approached” step mentioned by the reviewer. Following this, the researcher discusses that study with the patient, at which point they can agree not to participate. Those who agree to participate are then invited to a “consent
and screening” appointment at which time their participation in the trial is formalised by a written consent process.

This way of describing the trial is most in keeping with the flow of appointments that the patient has and is for their benefit.

Comments

16. In the write-up of the results, the authors will need to be clear that the results do not generalize to all patients with stage 1-3 CKD, only those with declining eGFRs or albuminuria.

Thank you for this suggestion. The reviewer is correct. This study is not powered to show any definitive results and the analysis, as well as being descriptive, will be purely exploratory.

Reviewer #3:

a) size of the introduction; this runs for about 5 pages and should be reduced in size somewhat

This has been reduced as suggested.

b) the authors should more clearly explain to the audience that four measurements of eGFR may not be sufficient to detect an effect of the intervention of the rate of decline in renal function. This could have been feasible if they only recruited rapid progressors (conventionally set at delta-eGFR at 5 ml/min/1.73m2 per 1 year), but from the inclusion criteria (criterion 4), it would seem to me that they may end up with patients who do not decline as fast. This should be qualified and quantified in the text

Thank you for this comment, we have revised the text to try and reflect this.

c) I find the inclusion of a section about "success criteria" somewhat superfluous

This section has been removed.