Author's response to reviews

Title: Baseline characteristics, statistical analysis plan and feasibility for the 'Prevention Of Decline in Cognition After Stroke Trial' (PODCAST) trial

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Author's response to reviews: see over
Dear Editor,

Thank you for your letter regarding the submission of our manuscript entitled Baseline characteristics and Statistical Analysis Plan for the ‘Prevention Of Decline in Cognition After Stroke Trial’ (PODCAST) trial (MS: 1523029833160017)

Here we respond to the reviewers’ comments.

**Reviewer 1**

1. The title should reflect what this paper is: it should mention that this is an assessment of the feasibility of the main phase – currently this first appears in the conclusions of the abstract

We have amended the title.

**CHANGE**

2. Once the title is fixed, the rest of the paper should flow from it. For instance, if this is a paper about assessing feasibility, then the planned Methods and appropriate Results for assessing feasibility should be included. If the title contains the statistical analysis plan (SAP), then the Methods and Results should describe this. A full SAP should be included in the body of the paper, and not just as an appendix without further comment (the current appendix is not an adequate SAP – it is missing much of the detail that is normally in a SAP). If the title is about baseline data, then the Conclusion should say something about whether the data were as expected.

We have changed the flow of the paper, in part. We have left the SAP as an appendix otherwise it makes the paper too long.

**CHANGE**

3. The interim analysis results have already been made public, apparently according to the Statistical Analysis Plan. This Statistical Analysis Plan should be presented here, so that the reader can be reassured that the SAP was finalised before the results were made public (and also because a Statistical Analysis Plan was promised in the title).

The SAP is presented, as an appendix (as above in 2). The first draft of this manuscript was written on 27/6/13, and the SAP added on 14/8/14, i.e. well before final follow-up, data cleaning and any analysis. Unfortunately, gathering co-author responses, submission, and two cycles of reviewer comments have meant that the analysis is now done. But the senior author/Chief Investigator guarantees that the SAP antedated analysis.

**NO CHANGE**
4. Table 3. Spell out IS in the footnote.

IS is ‘ischaemic stroke’. This is added to table 3.

CHANGE

5. The trial has only a small number of participants, yet the results are going to be adjusted for several covariates. It might be worth adjusting instead for a propensity score, as suggested in: E. J. Williamson, A. Forbes, and I. R. White. Variance reduction in randomised trials by inverse probability weighting using the propensity score. Statistics in Medicine 33:721-737, 2014.

We thank the reviewer for their suggestion. However, the SAP was set before data lock so we cannot now change the primary and other analyses.

NO CHANGE

6. The paper says that the trial ran in primary and secondary care, yet the protocol only mentions secondary care (as far as I can see). Was there a protocol amendment relating to this?

Intensive BP lowering and/or lipid lowering (as randomised) was delivered in secondary care at research clinics. Guideline interventions were delivered in general practice. This is clarified in the text under Methods/Interventions.

CHANGE

7. It is slightly misleading to say in the abstract that 83 of 100 planned patients were recruited. It was really 83 of 600, and the target was reduced down when recruitment was not as expected.

We have amended this in the manuscript’s abstract.

CHANGE

8. Could the information copied from the Protocol (in the Methods section) be shortened, to leave more space for new information?

We have edited the methods section but have left in sufficient detail for the reader to understand the trial’s design prior to reading the section on baseline characteristics; this improves the paper’s flow.

CHANGE

Reviewer 2
1. Abstract, introduction. It would be helpful to the reader to have a sentence in the Background clarifying the specific focus of the current paper.

The final sentence in the Background section now clarifies this point.

CHANGE

2. Abstract, Methods/Results. The maximum total scores of the ACE(/100) and MoCA(/30) should be given. The definition of the figures in brackets eg (sd) would aid clarity.

This information is added in the abstract and results sections.

CHANGE

3. Abstract, Methods. The time at which the primary outcome was to be measured should be given.

This is added to the Methods/Primary outcome section.

CHANGE

4. Abstract, Results. The NIHSS and Rankin should be given as important characteristics of the trial population.

We have added the data for mRS, but not NIHSS for space considerations.

CHANGE

4. Methods. I am not sure if I have misunderstood but under interventions, it states that all patients were randomised to intensive vs guideline blood pressure lowering and yet later it appears that only 300/600 total participants were to be recruited to the BP group.

We have clarified this point in the Methods/Interventions section of the paper.

CHANGE

5. Eligibility. Not all readers will be familiar with the telephone MMSE, it would be helpful to give the maximum achievable score and the cut-off considered indicative of dementia (ie the score equivalent to <24 in face-to-face testing). Telephone scores of 17 would appear quite low – how was dementia excluded in eligible patients? I understand the DMS-IV criteria were used but how were these criteria applied in practice?

We have included a description of how the scores on the t-MMSE compare to the face-to-face MMSE and provided a reference.
The t-MMSE has been compared to the MMSE and shown strong correlation. A score of 16 on the t-MMSE equates to a score of 19 on the MMSE. A score of 26 on the MMSE equates to a score of 23 on the t-MMSE (Newkirk et al., 2004). Please see Methods/Secondary outcomes.

6. Conclusions. The numbers quoted for dementia at 1-year post-stroke from the literature include patients who develop dementia early after stroke whereas in the current trial, these patients are excluded. Given that the post-stroke dementia risk is relatively low after the immediate post-stroke period, any treatment effect might be expected to be small. Further, the available data do not show a strong association between vascular risk factors and post-stroke dementia. Finally, the NIHSS and cognitive scores show that the trial population had mild events and were relatively high functioning thus further reducing the risk. Some discussion of these issues in relation to the risk of dementia in the trial population and in relation to the earlier statement made by the authors that the inclusion/exclusion criteria were designed to select a high risk population would be helpful.

We thank the reviewer for these comments but suspect they may be more appropriate for the main publication, if the trial is neutral, since the final results are not presented here.

7. References. Refs 8 and 9 appear to be duplicates.

We have checked and removed duplicate references.

8. Table 3. How was “memory problem” defined?

This was decided subjectively by the investigator based on discussion with the patient and informant, and any available information from the hospital records and GP.

9. Protocol references. The references for the telephone MMSE should be given. Also the references should be given for the validation of the ACE-R in cerebrovascular populations (particularly since this is the main outcome measure) and also for the MoCA and TICSm (there are more recent refs than the one given for TICSm) since all these tests were in fact developed and originally validated in non-vascular populations. The cut-offs used should be justified with some background information.
The telephone MMSE reference is included, as is a reference for the validity of TICS use in post-stroke population. Information on ACE-R is added in Methods/Primary outcome, and on MMSE, MoCA and TICSm in Methods/Secondary outcomes.

**CHANGE**

10. Please clarify how the IQCODE was used, the instructions are confusing - the protocol would suggest that the informant compares how the patient is now with how they were at the last follow-up but also suggests they make the judgement over the past year. The original IQCODE requires that the informant compares how the patient is now with how they were 10 years previously. The IQCODE method described in the paper would thus appear to be significantly different from the original – has this been validated? The change from the original should be acknowledged and discussed.

We thank the reviewer for this comment. Since the trial did not have a single follow-up time point (patients were followed for a minimum of 6 months but typically longer) and we did not know how long they would be in the trial for, we did not have a specific time at which to perform the IQCODE. Hence, the protocol required it to be measured at each visit. This approach, whilst not ideal, is a balance between what is ideal and what is practical. The present baseline paper is not an ideal place to place this explanation.

**NO CHANGE**

11. The proposed statistical analysis plans would appear appropriate and take into account confounding and adjustment for multiple comparisons.

We thank the reviewer for this comment.

**NO CHANGE**

**Reviewer 3**

1. The background section should be revised to ensure clarity that lowering BP and lipids, and antithrombotic therapy reduce ischaemic stroke recurrence following ischaemic stroke. Accordingly, the trial assessed BP and lipid lowering in ischaemic stroke, and BP lowering in ICH. This clarity is provided in the abstract, but not the background.

We have clarified this point in the Background.

**CHANGE**
2. The reviewer is not persuaded that the information presented in the manuscript from the start-up phase meant that the main phase was impractical using the agreed protocol, as implied in the conclusion to the abstract and the manuscript. Whilst the recruitment rate was indeed low, it would seem that approximately 50% of those screened were recruited. Outcome data are not provided to make an informed decision about other protocol aspects, e.g. target BP and lipids, cognitive assessment by phone or in person, etc. Clearly, the excess treatment costs are an important aspects but changes in their provision and the availability of generic atorvastatin, may mean that this aspect is less problematic now. Therefore, it would be helpful to have clarity around the exact reasons to support this statement.

We have clarified the statement in the Discussion and Conclusions section (paragraph 1).

CHANGE

3. Whilst the manuscript refers to secondary and primary care sites, this reviewer’s interpretation of the site list is that these were all secondary care sites. It would be useful to have the author's comments on whether this was partly the reason for failure to meet the recruitment targets, as this might be potentially addressable in a future trial.

See Reviewer 1 point 6 above. Hospitals are the ‘gate-keepers’ for most strokes so recruiting from them is efficient since they see the majority of patients. In principle, primary care could be used as PIC sites but this would probably add little for a trial with a fairly narrow time window that is proximal to the stroke onset. This might be relevant to the Discussion in the main paper, depending on results.

NO CHANGE

4. Minor Essential Revisions

1. Section May 2012, Bullet point 8, Line 4: 'Infarcts' misspelt

This spelling mistake has been corrected

CHANGE

Editorial requests:
Please include the names of all ethical bodies that approved your study in the various centres involved. If you do not wish to list them all in the Methods section, please include the list as an additional file and refer to this in the Methods section.
This is given in the list of recruiting sites towards the end of the manuscript. Those sites that gave ethics approval but did not recruit are not listed.

NO CHANGE

4. Please include a Discussion section after the Results section in your manuscript. The Results and Discussion may be combined into a single section or presented separately. Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals. The Results and Discussion sections may also be broken into subsections with short, informative headings.

We have separated the Results and Discussion section.

CHANGE

5. Please include an Authors’ Contributions section at the end of the manuscript, after the Competing Interests section. Each author needs to be listed individually. We suggest the following kind of format (please use initials to refer to each author’s contribution):

?AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript?

This is now included.

CHANGE

4. For additional files, please ensure that you list the following information after your reference section in your manuscript:

We have checked that the labelling of additional files meets the requirements of the journal.

Yours sincerely

Daniel Blackburn Philip Bath