Author's response to reviews

Title: The PACE Study: A randomised clinical trial of cognitive activity (CA) for older adults with Mild Cognitive Impairment (MCI)

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Dr. Barry R Davis
The Trials Editorial Team

Dear Dr. Davis

RE: The PACE Study: A randomised clinical trial of cognitive activity (CA) for older adults with Mild Cognitive Impairment (MCI)

Thank you for your prompt response and for offering us the opportunity to address the helpful comments of your reviewer, as outlined below:

**Major comments**

1. This is a clearly written manuscript of a competently designed and important RCT. I am concerned, however, that the trial will in the event lack power, since the target effect size is so large (80% power to detect a difference of 0.5 standard deviations). In itself this is not an argument against publishing the protocol – indeed, it is if anything at least as important to record such an effect size. The question is rather that there is no real justification and rationale for such a difference in terms of its plausibility or the importance of the points score difference that it corresponds to – both of which will be important in interpreting the between-groups confidence intervals that accrue, whatever the underlying power turns out to be.

**REPLY:** The reviewer is correct in stating that there is currently no reliable data that could be used to calculate the sample size of the proposed trial. For this reason, some inferences had to be made, although our previous research suggests that the effect sizes outlined in our protocol are consistent with other interventions that have been used successfully to treat people with MCI (Lautenschlager et al. JAMA 2008; Sep 3;300(9):1027-37). Currently available data suggests that older people living in the community lose 1.6 points per year on the CAMCOG (Cullum et al. Int J Geriatr Psychiatry 2000; 15:853-62). With 64 people in each group we will have 80% power to detect a between-groups difference of 1.5 points. This assumes a decline that is twice as large in the educational compared with the cognitive intervention group, and although statistically this may be associated with moderate effect size, it is the minimum difference that one might consider clinically significant.

2. Further practical details of randomisation are needed, especially in terms of communication of the identification numbers and allocations between research staff and whoever (or whatever system) was responsible for running the process/list.

**REPLY:** The allocation list has been handled by an independent investigator (OPA) who has no contact with study participants and is not directly involved in the supervision of staff responsible for the collection of data. The allocation table was then passed on to the investigator running the intervention (MV), who invited eligible participants to join the relevant groups. Research assistants undertaking the follow-up assessments remained blinded to group allocation. We have added this information to the section on “Randomisation” on page 15, paragraph 1.
3. The data analysis looks well planned but in the context of the modelling the primary outcome (i.e. what and when) should be clearly specified for the primary analysis.

REPLY: Changes in the CAMCOG score from baseline are the primary outcome of interest in the study. We will model these changes at 3 time points: 12 weeks (immediately after the intervention comes to an end), 52 and 104 weeks. We will use mixed effects models in the analyses of the data and will use imputation by chain equations (ice) to complete our intention-to-treat analysis. We have added this information to the text on page 15, paragraph 1 in the “Analysis of the data” section.

4. Page 12 line 2 and the title of the table – at both these points it should be stated explicitly that the follow-up times were relative to randomisation.

REPLY: The 12 and 24 month follow-up assessments were undertaken relative to the baseline testing. These changes have been introduced to the text (page 12, paragraph 3) and the heading of the Table.

5. Some comment would be helpful regarding how effective the authors expect the Education Group (the comparator) to be, especially since it seems to have a number of components that might well have an impact on at least some of the secondary outcomes.

REPLY: We accept that participation in the cognitively non-specific educational intervention is likely to have an effect on the performance of participants. However, to ensure continued participation in the control group we deemed it crucial to provide some form of intervention or potentially face differential drop out, with the control groups participants withdrawing because of lack of engagement in the study. We will model changes over time for both groups and this will enable us to determine the effect of both interventions (as well as the sustainability of this effect over 24 months) on cognitive performance. We have included reference to these points in the final paragraph under “Analysis of the data” on page 16.

Minor comments

1. Trials will have its own house-style regarding spelling of “randomised/randomized” (used variously in the manuscript) and “program/programme”, but the instances of “randomised control trial” should be “randomised controlled trial” throughout. On page 7 line 4 the semi-colon should be a comma, as in “… full PHQ[12], an instrument used …”. In the second sentence of the Recruitment of older persons section (last line page 5) “semi-structured interview” rather than “semi-structure interview”. The paper was generally well written although I found the phrase “multimillion-dollar business” too colloquial. The tense used is a bit variable between the past and future, and could do with some attention.

REPLY: These comments have been reviewed and the grammatical issues addressed throughout the manuscript.
2. On page 9 (Baseline Assessments) it would be helpful if it were stated explicitly here that these were conducted before randomisation. Did all of the battery of tests really only take 60-90 minutes to complete, even with breaks?

**REPLY:** All baseline assessments were completed before the randomization. This is now explicitly stated on page 9, under the sub-heading “Baseline Assessment”, paragraph 1. The baseline and post intervention assessments were completed within a 60 to 90 minute time frame (even with the provision of short tea breaks). A two hour window of testing time was provided for the 12 and 24 month follow up assessments to allow for the re-administration of the CERAD and to review the questionnaires.

3. Page 12 – how will the fidelity assessment be undertaken?

**REPLY:** A random set of the 220 audio-taped sessions was generated (44 in total). These have been transcribed and an independent rater used a scale to rate session content according to a criteria devised to review the consistency of the concepts/issues raised across each of the sessions. This explanation has been added under “Intervention” on page 12.

We would like to take the opportunity to once again thank the reviewer for his constructive comments which we believe have contributed to improve the quality of our report. We thank you for considering the revised version of the paper for publication in Trials and look forward to hearing from you.

Yours sincerely

Mandy Vidovich
(on behalf of the PACE study Authors)