Author's response to reviews

Title: Clinical efficacy and prognostic indicators for lower limb pedalling exercise early after stroke: A pilot randomised controlled trial

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Author's response to reviews: see over
To:
Editors-in-Chief: Doug Altman, Curt Furberg, Jeremy Grimshaw and Peter Rothwell
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Re: Clinical efficacy and prognostic indicators for lower limb pedalling exercise early after stroke: An early phase randomised controlled trial; MS: 1757957420466908

Thank you for your peer review of the above submission. We are most grateful for the reviewer’s very useful comments.

Reviewer’s introductory summary: The study protocol describes a small scale randomized trial for the potential effect of upward pedaling (UP) exercise in the early phase of recovery after stroke. The reported study aims are 1) to determine prognostic indicators of ability to execute UP and benefit from this exercise and 2) to obtain preliminary data on the efficacy and safety of the UP exercise to justify proceeding to testing with subsequent larger trials.

Response: To clarify, the name of the intervention is “Upright Pedalling (UP)” and not Upward Pedalling.

Our responses to the major comments are listed below, the reviewer’s comment is listed first followed by our response. Points are numbered as per the reviewer’s points for clarity:

1. The authors should use the term “pilot study” in their title. Even still, there should be some evidence that the data is likely to be adequate to address these preliminary aims. For example, this could be done by calculating the precision of the outcome estimates in each of the treatment groups.

Response: We agree with the reviewer that “pilot study” is a more accurate title. We have thus amended the title of the study to “......pilot randomised controlled trial” We will express 95% confidence intervals for outcomes in the intervention and control groups and should any further clarification be required on precision of outcome estimates, we will be very happy to do so.

2. I don’t believe that the first aim of the study is matched by the analysis plan. The authors appear to make a claim, in several sections of the manuscript that they will be predicting indicators of treatment response. Determining who benefits from a therapy generally requires looking at interactions with treatment, and typically requires a much larger sample size than determining a treatment effect overall. It is unclear how this pilot study will be able to address such an ambitious aim at all. Rather, in the statistical analysis plan, it appears that the prognostic markers will be used to predict “ability to pedal”. This appears to correspond (in figure 1) to one of the criteria for randomization. It is unclear how this dependent
variable has any relationship to response to therapy, and—more to the point—it is unclear that predicting this is of any use, since the characteristic is readily ascertainable clinically without the need to use a highly imprecise prediction tool.

Finally, the authors may be interested in predicting “response to UP” indicating some change in baseline among the 12 patients in the treated group. Again, this does not seem to be particularly feasible or useful, since the numbers in that treatment group will be very small and their prognostic model will be selecting more mildly affected patients rather than those most likely to benefit. Thus, the authors need to be clearer about what their first aim is (i.e., what is it they are trying to predict) and what usefulness the prediction will have, or they should consider abandoning the aim. They should also demonstrate the adequacy of the data regarding the aim, bearing in mind that a “rule of thumb” for multivariate prediction is 10 outcomes per independent variable.

Response: In the light of the reviewer’s comments, it has come to our attention that the aim of predicting response to pedalling was left in the protocol from an earlier version and we apologise for misleading reviewers on this point. As suggested by the reviewer, this part of the aim has been removed from the relevant study aim and throughout the manuscript as we agree entirely that it is neither feasible or useful, for this pilot study.

We believe that there may have been a misunderstanding regarding the characteristics of stroke survivors to be included and apologise if this is not clear. The reviewer suggests that we will be selecting “mildly affected patients”. It is hoped that our inclusion criteria make it apparent that we are seeking to include patients with substantial deficit early after stroke; our 4th inclusion criteria is that participants will score only 0, 1 or 2 on the Functional Ambulatory Categories, meaning clinically that they will be unable to walk, or need considerable help to do so.

3. Can the authors provide any information on what corresponds to a clinically relevant change on the primary outcome (Motricity Index)?

Response: To the best of our knowledge, nothing has been published on the minimally important clinical change for the Motricity Index. However, we would consider a change of two levels, for example moving from palpable muscle activity only to movement through range against gravity, to be a clinically important change.

4. The primary outcome will be recorded after the completion of the intervention whereas secondary outcomes (EMG-based ones) will be recorded throughout. This introduces the risk of missing outcome data in this already very small trial. Conducting the primary outcome measurements after each training session would ensure no missing data.

Response: It is standard practice in RCT’s to minimise the possibility of learning effects and we would therefore seek to use the Motricity Index only at baseline and outcome. However, EMG data will be recorded daily and this will provide important information about biological change on a daily basis which is unlikely to show a learning effect as no feedback of EMG activity will be provided to participants.

5. It is unclear why the 10min duration of exercise was selected. A previous, unpublished observational study is cited regarding safety of a 10min exercise, but no human data for expected efficacy of this duration of intervention is reported.

Response: We agree with the reviewer that the best data available comes from this earlier observational study, which supports the need for the current early phase pilot study. It is
hoped that this pilot will provide further information on exercise duration tolerated early after stroke to potentially inform larger trials, as per the MRC guidance on evaluating complex interventions.

6. The order of secondary outcomes should match the study aims order. According to the aims section of the manuscript, the prognostic study appears to be the primary aim of the study. It is not entirely clear what outcome will be used for this aim. Also, if the authors intend to use changes from baseline, this should be specified, and accompanied by an appropriate analysis plan.

Response: We agree that the order of the primary/secondary outcomes is ambiguous. The reviewer is correct that the prognostic part appears to be the primary study aim and it is not. Thus the manuscript sections on outcomes and aims have been fully amended accordingly to reflect the appropriate order.

Thank you very much for considering this response to the review of our manuscript. We look forward to hearing from you.

Yours Sincerely

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