Reviewer's report

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

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Reviewer: David Kent

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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.

Major comments:

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.

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.

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

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.

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.

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.