Reviewer’s report

Title: Evaluating the effect and mechanism of upper limb motor function recovery induced by immersive virtual reality-based rehabilitation for subacute stroke subjects: study protocol for a randomized controlled trial

Version: 0 Date: 15 Sep 2018

Reviewer: Cheney Drew

Reviewer's report:

Thank you for the opportunity to review this manuscript. Overall this is a generally well written manuscript and the study is an interesting look at improving rehabilitation in stroke patients. However, reading through I felt there were several areas where there was a lack of detail surrounding several aspects of the study. Further, many of the items on the SPIRIT checklist have not been detailed with no explanation of their omission. I have specified a number of areas below where further detail would improve the robustness of this manuscript as a protocol paper.

1) The title of the manuscript suggests that the use of immersive VR for sub acute stroke recovery is already effective. It may be worth re-phrasing the title to highlight that the effectiveness of VR is being investigated.

2) Items 3-5d on the SPIRIT checklist have not been completed and no reason for non-completion has been given. For transparency, these items should be described in the protocol.

3) The study objective could be made more concise. It should not be described as an aim because aims and objectives are different. I would also advise removing the 'design' aspect from the objective as this is written as a trial of efficacy and not of feasibility.

4) It is not clear from the manuscript why the comparator group has been chosen to be 'rehabilitation as usual' only. This does not control for the use of a novel intervention (VR) and so the design is not purely testing the use of immersive VR, but is also testing the effect of an additional intervention. Did the authors consider controlling for this by providing the control group with a non-specific VR experience/session? This would help reduce bias in the control group.

It would also be helpful if the authors could explain why they chose for the experimental group to have a combination of immersive VR and normal rehabilitation.

5) The study setting (Item 9 SPIRIT checklist) is not adequately described on p.5 Where is the intervention taking place? Is it in clinic? A rehabilitation centre? Please clarify
6) There is not enough detail concerning who will deliver the conventional rehabilitation and what constitutes this. I would suggest reviewing the TIDiER guidelines for the reporting of complex non-pharmacological interventions and using this framework to report the intervention.

7) How will the amount of conventional rehabilitation (not just length of session) be measured? If one participant puts in a lot of effort into their exercises and another participant puts in very little effort, how will that be recorded, if at all?

8) For the primary outcome measure- as there are multiple domains within the Fugl-Meyer assessment of upper limb motor function, will the primary outcome be a composite score of all the domains, or will a single domain be selected as the primary outcome prior to analysis?

9) The sample size calculation sample appears a little simplistic. It does not seem to take into account what would be considered a clinically relevant change in the Fugl-Meyer assessment and to what degree it would be expected for the control group to improve with conventional rehabilitation alone. I think this would benefit from some expert input from a trials statistician and should be revised accordingly.

I also struggle with the use of a sample size from an MRI study into neural mechanisms of chronic back pain to determine the required sample size for a study into the neural mechanisms of post stroke rehabilitation, although this may come from a lack of understanding of imaging studies on my part. Even if the imaging techniques have demonstrable change in the back pain study for that number of subjects; that does not automatically mean that you will be able to detect imaging changes in the same number of people recovering from stroke; the likely white/grey matter changes will be fundamentally different between the two cohorts. The authors need to explain the similarities in far greater detail to be understood by non-imaging expert audience.

10) Why is item 15 of the SPIRIT checklist not included? Is there a high enough throughput of eligible patients at the dingle site to allow recruitment to target within the recruitment period? Is this because this trial does not have any funding and as such is not subject to the usual time/funding constraints usually expected in a clinical trial?

11) There is not enough information on how the random sequence will be generated by the computer. Are there any balancing factors? Will the randomisation control for factors such as age/functional ability/indices measured by MRI?

12) There is no mention in the manuscript of any monitoring or auditing methods, either for monitoring data or oversight of the trial in general.

13) There is no indication of who within the study team will be taking informed consent form the participants, or who will be making the assessment of eligibility with regards to capacity. This should be included.
14) The authors should also include a statement about how participant's confidentiality is protected (if at all) via, for example, anonymisation of data.

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