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

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Reviewer: Michelle Johansen

Reviewer's report:

Huang et. al propose a randomized controlled trial to investigate the "effect and mechanism of upper limb motor recovery induced by immersive virtual reality-based rehabilitation for subacute stroke subject." In this proposal, the investigators aim to: 1) Assess the efficacy of immersive VR based upper extremity rehabilitation in subacute stroke patients 2) Explore underlying brain mechanisms of VR-based rehabilitation. Task specific motor learning is an area of much interest in Neurology and more trials are certainly needed in this area, however there are areas in the current proposal that warrant improvement prior to undertaking.

Below are specific comments for the investigators by sections of the grant as well as a general summary of the study at the conclusion of the review.

Abstract:

1) The investigators should use caution when utilizing the word efficacy, particularly in the setting of clinical trials as the reader will immediately think of efficacy vs. effectiveness trials, and given that efficacy trials normally reflect a highly selective homogeneous population with several exclusion criteria, this term wouldn't be the best reflection of the proposed study.

2) It would be helpful to define non-immersive in the abstract, as those not familiar with this area will not understand the difference

3) The investigators would do well to include the timing of intervention (specifically when the intervention will begin post-stroke and when it will conclude post-stroke, the enrollment window and the treatment window) in the abstract. As written, "over a 3-week time period" feels vague.

4) The term brain reorganization should be defined in the abstract as it is an outcome of interest

5) Again, it would be helpful to define the timing of the scans. Does before rehabilitation mean that a scan one year before rehabilitation would be permissible?
6) The discussion focuses on the 2nd aim, but does not mention the 1st aim. How will efficacy be defined?

Introduction:

1) Regarding stroke incidence, it is not increasing in all areas across the globe. One would recommend caution in making such statements.


2) It would be helpful to cite current literature that discussed the outcomes of what is the current norm. For example, how effective is current traditional upper limb rehabilitation?

3) There has been some controversy surrounding constraint induced movement therapy and its true improvement in upper limb function. This literature should be acknowledged.

4) The summary on page 4 is well written and helps set the stage for the study. It could be further improved upon by defining what neural mechanisms of recovery are specifically being targeted in this approach.

5) Why are subacute stroke patients being targeted? This should also inform some of the background information for the proposal.

6) What is the hypothesis for this clinical trial?

Methods:

1) Please define how efficacy is being assessed or defined in the study. This should be information that is included early in the proposal and is essential when considering power calculations for a study.

2) When writing a trial protocol, it is helpful to use proper clinical trial terminology. Specifically, when mentioning that randomization will occur evenly, does that mean 1:1?

3) How was the number for 60 subacute stroke subjects determined? What was the literature that formed this power calculation?

4) What will form the basis of the 3-week conventional rehabilitation program? As this is the control arm, it is important to define this carefully. Later it is mentioned that 60-minutes of conventional rehab training per day is specified, but will this be the same in all 30 patients? Will it be only targeting the affected upper limb? How much time will be spent doing each activity?
5) What is the self/clinician filled questionnaire? Will there be two questionnaires? The participant and the clinician may have very different view of the progress of a participant.

6) The flow diagram is helpful but needs to be improved upon by defining the post-training assessment. As this is a main outcome of interest, the definition by this point in the grant is still unclear. Later it is defined as the Fugl-Meyer score.

7) Inclusion criteria state that Brunnstrom stages 1-3 will be considered eligible for enrollment. Stage 1 is flaccid paralysis. How will participants be able to participate in VR if they are completely flaccid?

8) Given the small sample size, it does not appear prudent to allow for participants to use the unaffected side limb to help with participation in the tasks. This would form an area of great concern when assessing the outcome.

9) There are numerous outcome measures on such a small group of patients with multiple time points. Once again, the power calculations should reflect this if all outcome measures are kept. The data that appears to have been used by the team is those with chronic back pain, is this a fair comparison to those with stroke, who will already have some degree of brain damage?

10) Size and location of stroke will be a great determinant when considering the outcome of the trial. Was stratification considered? How will this be accounted for in adjustment models?

Discussion:

1) In the discussion, the authors appropriately recognize sample size as a limitation and the need for multicenter, large-scale trials. Yet this is followed by a statement regarding feasibility and efficacy, while the proposed trial does not include feasibility as an outcome.

Summary:

The proposed study is an area of interest and much active research, particularly given task based learning following stroke and the unique utilization of functional MRI. However, the trial is limited in its description of its outcome measures and would be greatly improved upon by carefully defining the outcomes; specifically efficacy, self/clinician questionnaires and changes in neuronal network. The sample size proposed for the trial, particularly when considering multiple outcome measures and the literature considered, does not seemingly compute and should be revisited.

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