Peer-review Comments and Author Responses

Reviewer 1

1. *Major comments: Great paper! Please see my comments in the document attached.*

Thanks for the comments, adjustments and careful review. We hope the revised version is adequate and are more than available for any additional adjustments.

Reviewer 2

Major comments

2. *Dear authors, I want to congratulate you on the quality of your manuscript and I believe this method proposal article is strongly significant and novel. I also would like to point there are a few minor corrections to be made. It will be a pleasure to reanalyze the paper after your reconsideration. I specify some points:*

Thanks for the comments. Below we respond to all comments and hope that the revised version is adequate. We are more than available for any additional adjustments.

Minor comments.

3. *Title: it is clear, though it can be challenging for non-specialists to understand.*

Thanks for the comments. We adapt the title so it will be more objective.

4. *The primary and secondary outcomes need to be specifically mentioned in the methods.*

Thank you for your comments. We adapted and highlighted the change in line 154 – 158.

5. *The item "exclusion criteria" is misnamed as "inclusion criteria".*

Thank you for highlighting this mistake.

6. *I believe the time from diagnostic to evaluation must be better defined.*

Thank you for your comments. The time from diagnostic to evaluation was not defined, however it will be considered in the analysis. We would like to evaluate if adaptations developed by patients with more time between diagnostic and evaluation will be able to be observed by the new method proposed.

7. *As the reader can be a nonexpert in the field I believe that a better explanation of the eye tracking relation with the Armeo Spring exoskeleton must be made (what is specifically done by the eye tracking?).*

Thank you for your comments. We adapted and highlighted the change in line 339 - 344.

8. In line 299 the word consists should be in the plural.

Thank you for highlighting this mistake.

9. In line 417 the word "de" should be written "the".

Thank you for highlighting this mistake.

Reviewer 3

Major comments

10. Dear authors, congratulations on the innovative initiative, it has candidly been a pleasure to review this manuscript. However, there are some few minor revisions that need to be addressed before publication on the "Principles and Practice of Clinical Research (PPCR) Journal".

Thanks for the comments. Below we respond to all comments and hope that the revised version is adequate. We are more than available for any additional adjustments.

Minor comments

11. Include Brazil stroke incidence and prevalence rates, comparing them to those from other Latin American Countries.

Thank you for your comment. We added the data 55 -63.

12. From a general perspective, it is a little confusing to read the introduction. I recommend rearranging the order of the paragraphs, since it may only consist of three paragraphs:

- *General background of stroke and sequelae – Including incidence and prevalence rates from a worldwide and national scope.*
- *Gap in knowledge – Referring to the difficult clinical applicability of currently recommended tests and scales for cognitive decline assessment after stroke.*

- *How you will fill that gap in knowledge – Use of eye tracking to identify components related to cognitive deficits and other stroke sequelae.*

Thanks for the comments. We completely revised the introduction in order to make it clearer and more objective.

13. Overall, it is a coherent and informative introduction, however, its length and order make it hard to read. Many of the information can be transferred to the Discussion.

Thanks for the comments. We completely revised the introduction in order to make it clearer and more objective.

14. Regarding sample size, it will be defined after its estimation using GPower3 software; however, I advise using the largest sample possible, to validate any statistical findings.

Thank you for your comments. The aim of this study is to evaluate the feasibility, so we could assess the methodology through a pilot study. After that another study will be developed with a bigger sample to validate any statistical findings.

15. Regarding the inclusion criteria, I recommend specifying:

- *Modified ranking scale (mRS) range.*
- *Therapeutic endovascular approach (mechanical thrombectomy, balloon angioplasty, thrombolysis and so on), since it can significantly affect the postoperative evolution of the patient.*
- *Preoperative and postoperative NIHSS scale range.*

Thank you for your comments. The study aims to evaluate a new method for diagnosing cognitive impairment after stroke unrestrained the size and location of the lesion, treatment, and physical impairment. For this reason, we chosen to not delimit the patients by those scales.

16. In conclusion, this is an outstanding approach to assess neurological deficit in stroke patients. I highly recommend its publication in the PPCR journal since it will guarantee to maintain its excellence and novelty.

Thank you for the kind and encouraging comment.

Reviewer 4

Major comments

17. The manuscript is detailed, but certain sections could benefit from improved clarity and organization. Consider breaking down LONG paragraphs into smaller, focused ones to be friendly with the reader. There's some repetition in the introduction and methods section. Review and eliminate redundant sentences or phrases to improve the flow.

Thanks for the comments. Below we respond to all comments and hope that the revised version is adequate. We are more than available for any additional adjustments.

Reviewer 5

Major comments

18. The manuscript reports a methodology of assess motor and cognitive components of patients with stroke. through a new technology used with Armeo Spring. The authors demonstrated that this methodology is valuable, feasible and relevant. However, introduction is too long. There are 1280 words only in the introduction. So, I recommend an introduction more succinct. Despite the writing being elegant, it is difficult to understand how Armeo Spring works or basic aspects of its structure. Therefore, I suggest a figure that illustrates its structure or outlines the main points of its operation. The authors the authors cited results from their own experience, it would be very interesting compare with already published examples and remember pros and cons. In this way, the authors should be a more practical and could give greater emphasis to these aspects of the functioning of Armeo Spring.

Thanks for the comments. Below we respond to all comments and hope that the revised version is adequate. We are more than available for any additional adjustments.

Reviewer 6

19. General comment

Dear authors and editor,

The study protocol offers a clear framework for conducting a pilot test to explore whether eye-tracking-assisted VR gaming can effectively assess cognitive function in stroke patients. I have several kind suggestions to propose after reviewing the protocol.

Thanks for the comments. Below we respond to all comments and hope that the revised version is adequate. We are more than available for any additional adjustments.

Major comments

20. Update the first paragraph's references to more current ones if possible. The epidemiologic background should be written with the most up to date data available.

Thank you for your comment. We added the data 55 -63.

21. While this study represents a pilot investigation with a small sample size, the inclusion criteria appear rather broad. Notably, the presence of motor functional deficits in patients after a stroke could have different presentations depending on the affected area of the brain. Focusing solely on hemiparesis without accounting for the specific location of the brain injury might complicate the assessment and control measures within the study, particularly concerning non-motor cortical injuries. For instance, distinguishing between patients with clear motor cortex injuries versus those with impairments impacting visual pathways or resulting in apraxia/agnosia could help make the results of the study's initial results in order to propose the larger subsequent studies.

Thank you for your comments. Since the study explores a new method to evaluate cognitive impairment that most of the time is underdiagnosed, we chose to not restrain patients with known impairment.

22. *The scales and tests recommended for cognitive assessment are repeated in the introduction and methods section. To avoid reiteration, there could be only one mention of the entire test list. Then explain the chosen tests and give the reasons on why you picked them.*

We thank you for the comment and agree that the description was confusing, even though the description in the introduction represents recommendations from the international community and the description of the method represents the instruments used. In any case, we excluded the description of the introduction, keeping only that of the method.

23. *It still wasn't clear if all of the chosen tests for this study would be done on every single subject or if instead the tests done would be chosen on a case-by-case basis based on each patient's needs for their symptoms and limitations.*

Thank you for your comments. We adapted and highlighted the change in line 200.

24. Regarding the feasibility analysis, it is important to take into consideration that if every patient is going to have to do all of the tests, the results might lack external validity, since this would be really hard to implement in real clinical practice and choosing a few tests would make the study more feasible overall. Furthermore, to streamline the study steps, an alternative approach involving the real-time use of a stopwatch during sessions by the therapist, or a third-party observer could be a pragmatic consideration, potentially preventing the need for post-session video review. Finally, specify if the intention of the third paragraph is to state that there will be an acceptability measurement conducted in the study. And specify how acceptability is going to be measured, with more context than just possible answers.

Thank you for your comments. We agree with the discussion raised. However, once tested, this method will seek to explore how the use of the combination of Eye Tracking and the exoskeleton is associated with cognitive assessments, typically carried out through tests and questionnaires. Furthermore, the method proposed here will be evaluated in the future in relation to the feasibility of its use. In terms of feasibility, we did not seek to assess whether the complete assessment of cognitive tests + task with eye tracking and exoskeleton is feasible. Our aim is to evaluate whether the task is as effective as the combination of tests to measure cognition and evaluate whether we can actually run the tasks with the target audience. In other words, we do not need to assess whether it is feasible and cognitively exhausting for patients to perform all the tests + tasks with eye tracking and exoskeleton. We agree that all of these assessments will be unfeasible in clinical practice, which justifies the carrying out of the present study to evaluate whether it is possible to continue with the task with eye tracking and exoskeleton alone.

Minor comments

26. Line 58 improve the punctuation and clarity of the sentences

Thank you for highlighting this mistake.

27. Line 102 "eye's position"

Thank you for highlighting this mistake.

28. Line 143 remove dot

Thank you for highlighting this mistake.

29. Line 164 change same to "sample"

Thank you for highlighting this mistake.

30. Line 175 change to "exclusion criteria"

Thank you for highlighting this mistake.

31. Line 193 and 213 remove the word "still"

Thank you for highlighting this mistake.

32. Line 298 "consists on collection"

Thank you for highlighting this mistake.

33. Line 299 "to pop the balloons all over the screen"

We are sorry for this huge typo. We corrected this sentence properly.

34. Line 301 "the session's total time is 12 minutes"

Thank you for highlighting this mistake.

35. Line 305 SMI Eye Tracking glasses "are" an eye…

Thank you for highlighting this mistake.

36. Line 346, simplify to "presented in tables"

Thank you for highlighting this mistake.

37. Line 417 and 419 scream to "screen"

Thank you for highlighting this mistake.

38. Line 420 "game score"

Thank you for highlighting this mistake.

39. This study protocol proposes a relevant and important topic in neurology and stroke rehabilitation. I believe these suggestions will be useful for improving the quality of the

protocol and the resulting study. This should help provide the needed knowledge for the follow-up studies that are to be designed from the results of this initial trial.

Thank you for the kind and encouraging comment.