

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Effects of home-based mirror therapy and cognitive therapeutic exercise on the improvement of the upper extremity functions in stroke patients with severe hemiparesis: a protocol for a pilot randomized clinical trial.
<b>AUTHORS</b>	Gonzalez Santos, Josefa; Soto-Camara, Raul; Rodriguez-Fernández, Paula; Jimenez-Barrios, Maria; Gonzalez-Bernal, Jeronimo; Collazo-Riobo, Carla; Jahouh, Maha; Bravo-Anguiano, Yolanda; Trejo-Gabriel-Galan, Jose M

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Takatsugu Okamoto, MD Department of Rehabilitation Medicine Nishi-Hiroshima Rehabilitation Hospital Hiroshima , Japan
<b>REVIEW RETURNED</b>	24-Nov-2019

<b>GENERAL COMMENTS</b>	Cognitive Therapeutic Exercise (CTE) is one of the facilitation technique, but in this study there is no description of the training content and number of repetitive motion. It is also unclear whether therapists using the technique are constant in quality. Also, there is no specific description of what kind of training patients will be undergoing with Task-Oriented Motor Learning (TOML). The function, usage of upper limbs, and cognitive function are well evaluated, but the “compensation strategies” described in the introduction have not been evaluated. Unfortunately, it seems inappropriate for this journal.
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<b>REVIEWER</b>	Alex Street Anglia Ruskin University, UK
<b>REVIEW RETURNED</b>	17-Dec-2019

<b>GENERAL COMMENTS</b>	Dear authors, This look like an interesting study, much needed for those with severe UL hemiparesis. Please see the attached Pdf of your manuscript, which contains some comments. I don't think that these are major amendments. They are simply to help clarify your study design. If it works, it must be replicable. If this is a home-based study, then this should be reflected in the title and abstract. You should also add some literature on home-based upper limb studies. If this is a study for severe hemiparesis, which it is, then this should be in the title and clearly described in the manuscript. Again, link to the lack of research in this area, cite the relevant papers on severe hemiparesis.
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	<p>Please clarify that this is a single blinded, three armed parallel study and be consistent with this throughout</p> <p>The inclusion criteria and quite open. If there are subtle changes in UL function how will you measure these, the Fugl and ARAT may not detect anything? Secondary (cognitive) measures may show change.</p> <p>How are you screening for Aphasia, what is the threshold for exclusion?</p> <p>Sample size is stated, yet you describe how the power calculation will be performed.</p> <p>Make the research question clear in the abstract and throughout</p> <p>Clearly state the primary outcome measure and primary end-point (for example Fugl Meyer, week 13). In the abstract and methodology.</p> <p>Clearly describe the statistical analysis for the primary outcome data, t-test, ANOVA? Currently this is quite unclear.</p> <p>Be consistent with terms (BDLA, DLA, ADL).</p> <p>There doesn't appear to be a Cochrane review of UL RCTs. This, and the recommendations it contains must be cited (Poolock et al, 2013). You will find this and one for home-based interventions (I think) in the Cochrane library database.</p>
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<b>REVIEWER</b>	Marika Demers University of Southern California, United States of America
<b>REVIEW RETURNED</b>	21-Apr-2020

<b>GENERAL COMMENTS</b>	<p>This manuscript describes the study protocol for a randomized control trial aiming to determine the effectiveness of two distinct interventions, mirror therapy and cognitive therapeutic exercise both in conjunction with task-oriented motor learning, compared to a control group (i.e. usual care only) on upper limb function. This study could help guide stroke treatment by identifying the superiority of one intervention over the other. In the current context, the ability to deliver treatment outside the clinical settings is very promising. Well-designed, large randomized control trials are needed to help the field of stroke rehabilitation to move forward. The methodology for study is well-designed and the use of a reporting checklist ensured that key elements are reported in the study protocol. However, my main concern is with the quality of the English throughout the manuscript and the terminology used. This manuscript would benefit from being review by a native English speaker. Some of the terms used are not adequate and may have been mistranslated from Spanish? (for example, p.3, line 5, the word "liberty" is not appropriate in this context and should be replace by "independence" or p.7, line 57, "principal variable" should be replace by "primary outcome"). In addition, the terminology is not consistent throughout (e.g., upper limb vs extremity, follow-up vs. post-test). The International Classification of Functioning (ICF) could also be useful to describe the primary and secondary outcome of interests. For example, upper limb function at both the body function/structure and the activity levels should be the primary outcome measure, instead of the "upper limb functionality". The discussion should also be expanded to better describe what are the expected contributions from this work (aside from publishing the results), what knowledge will be gained by this study and the limitations. Finally, as a suggestion, the recent review by Stinear et al. (2020) about trials in stroke rehabilitation could help guide the authors in conducting this large randomized control trial (<a href="https://doi.org/10.1016/S1474-4422(19)30415-6">https://doi.org/10.1016/S1474-4422(19)30415-6</a>). I have outlined my detailed feedback below:</p>
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	<p>p.3, lines 17-19: The objective of this study should be clearly spelled out.</p> <p>P.3, lines 26-28: The acronym for daily life activities (DAL) should be replaced by ADL (activities of daily living) – a term that is more commonly used in rehabilitation.</p> <p>P.3, lines 28-29: It is unclear what the 3 intervention groups are. Please clarify that the study involves 2 intervention groups (mirror therapy + task-oriented motor learning and cognitive therapeutic exercises + task-oriented motor learning) and 1 control group.</p> <p>P.3, lines 31-33: Please specify the duration of the intervention. Maybe the first follow-up visit should be replaced by the term “post-intervention”, with the term “follow-up” could be used to describe the last follow-up visit done at week 13.</p> <p>P.3, line 47: The expected contributions from this work are missing (if the authors are lacking space, the ethical portion could be shortened).</p> <p>P.4, line 53-59: The stroke recovery process described here is inexact. Spontaneous recovery can continue to occur even after 1 month post-stroke, while experience-dependent recovery (also called plasticity) can occur immediately after stroke and throughout the rehabilitation process. There is a vast body of literature related to stroke recovery.</p> <p>P.5, line 7-10: The organization of the introduction does not allow the reader to understand why it is of interest to use Mirror Therapy and Cognitive Therapeutic Exercise. It is also unclear why both interventions are combined with task-oriented motor learning. Moreover, is TOML the same as task-oriented training, a common approach in stroke rehabilitation?</p> <p>P.5, line 28-31: From reading this sentence, I am questioning why mirror therapy is used in the current study, since previous work has shown that this intervention is not effective. Consider rephrasing this sentence to better nuance why mirror therapy is promising and the factors that may have contributed to the limited effectiveness.</p> <p>P.6, line 42-54: Consider rephrasing the study objective in a PICO (person, intervention, comparison, outcome and time) format. Also, study hypotheses should be presented with appropriate reference to the literature to support each hypothesis.</p> <p>P.7, line 21: Unclear what this sentence means. Consider rephrasing.</p> <p>P.7, line 34: Please indicate how the exclusion criteria will be assessed (chart review, clinical assessments, etc.).</p> <p>P.8, line 18: The interventions are described very broadly. It is difficult to assess what will be done during each intervention and whether participants are able to continue to receive their usual care (if what, what is part of the usual care). Understanding the key components of each proposed intervention are needed to</p>
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	<p>allow the reader to understand how neuroplasticity will be targeted by each intervention.</p> <p>P. 8, line 48: Consider using a picture of the experimental set-up to facilitate the understanding.</p> <p>P.9, line 17-49: This section requires extensive editing. I don't know what "first modality (first degree)" refers to. From my understanding, the authors are trying to describe how treatment will be progressed based on the level of motor impairments of the participants. The description of how treatment will be delivered for individuals with more severe motor impairments is vague (focus on decreasing spasticity by doing passive stretches? If I am correct, how it this still considered task-oriented training?).</p> <p>P.9, lines 50-52: Are all participants recruited at stroke onset? The follow-up visit is once post-intervention and then 2 months later? I understand that the recruitment for this study is already underway, but would it possible to do the follow-up visit at 6 month post-stroke (or 6 months after the initial recruitment to this study) to better understand the progress in individuals beyond the subacute phase of recovery?</p> <p>P.10, line 34: Please specify for which joint and which motion (e.g. elbow flexion). Why did you choose the Ashworth scale over the modified Ashworth scale?</p> <p>P.11, line 44: I am unsure if the assessors are blind or not. Having a blind assessor would make this study stronger.</p> <p>P.12, line 3: It is unclear if subgroup analyses will be performed. If this is anticipated, the plan to carry out a subgroup analysis should be provided.</p> <p>P.12, line 12: The word "qualitative" is misleading, since all outcome measures collected are quantitative in nature.</p> <p>P.15, line 3: Reference list contains many articles published in Spanish, when there is a wide body of literature from world-renown researchers providing background information about stroke and motor impairments. Please consider modifying these references.</p>
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## VERSION 1 – AUTHOR RESPONSE

### Response to Reviewer 1.

First of all, we would like to express our sincere gratitude for all comments and suggestions received from the Reviewer 1. This information has certainly enriched the text for its best understanding, thank you very much indeed. We have clarified the reviewer's questions. We have introduced the required changes both in our answers to the specific comments and in the final manuscript.

**Broad comments:**

**Cognitive Therapeutic Exercise (CTE) is one of the facilitation technique, but in this study there is no description of the training content and number of repetitive motion.**

**Response:** Thank you very much for pointing it out. Next, we explain the differences between the facilitation techniques and cognitive therapeutic exercise (CTE) as well as the references on which this information are based.

Facilitation techniques decrease the learning of abnormal movement patterns and allow the patient to practice normal movements from the initial stages. During facilitation, the practitioner continually establishes light and smooth contacts with key control points, manually assisting desired movement patterns. The professional is in charge of controlling the quality and characteristics of the movement, while the patient only limits himself to following the manual instructions and performing the assisted movements a repeated number of times.

In contrast, the CTE or Perfetti method is based on the neurocognitive rehabilitation Theory, in which it is considered that the recovery quality of the altered functions depends as much on the activated cognitive processes (attention, memory, perception, ability of solve problems, ability to imagine) and the modality of in which they are activated. The professional intends to obtain significant learning and therefore proposes a task as a cognitive problem that the patient must necessarily solve through cognitive activation. The exercise is proposed always following the same structure: first, a cognitive problem is proposed; then, a perceptual hypothesis or anticipation of the problem (feed-forward) is activated; and, finally, a process of comparison between the previous information and the sensory information is activated (feedback) that the patient receives during exercise.

Therefore, to solve the problem, the cognitive activation of the subject is always involved and the difficulty of the exercise is related to the motor aspects, but also with the level of cognitive activation, that requires sensory discrimination and cognitive organization during the performance of the homework.

Therefore, the importance of cognitive therapeutic exercise lies not so much in the number of repetitions that the patients are carried out during exercise, but in the cognitive processes that are activated and the way of activating them. This differentiates it from facilitation techniques that focus their attention on the repetition of an exercise that the therapist assists, without cognitive activation of the patient.

Regarding the execution of the technique, since the motor deficiency of the subject is not homogeneous, it is frequent that the recovery of the mobility of the different segments occurs with different magnitudes and therefore it is necessary to carry out exercises of different degrees.

All patients will begin performing first-degree exercise until they regain the ability to control the reaction to stretching so that intensity, temporality and spatiality can then be graduated. The patient is asked to recognize, with closed eyes, the characteristics of certain figures or the position of different body segments effected by the therapist. We are not allowed to make any voluntary contraction; we must limit ourselves to paying attention to the elaboration and verification of the perceptual hypothesis.

Subsequently, the second degree exercises will be carried out at the moment in which the patient has correctly carried out the first degree exercises, for a suitable period of time in order to control the reactions to stretching in a sufficiently automated way and when they begin to present with frequency indications of singular movements of the fingers and other body segments.

The main objective of this type of exercise is to guide the patient to acquire control of the effects of irradiation and to allow him to carry out active contractions and, consequently, to recruit a number of motor units.

Finally, a third degree exercise is carried out through which the patient will learn to adapt their movement to the proposed perceptual hypothesis once they have managed to automate the control of abnormal behaviors thanks to the second degree exercises. The objective of these exercises is to allow the activation of a greater number of motor units and to achieve recruitment in different temporal and spatial combinations. The criteria that must be taken into account to establish a correct programming of the exercises

depend on the configuration of the trajectories that are requested from the patient and on the intensity of the contractions that must be activated in the segments that execute them.

- Lee S, Bae S, Jeon D, Kim KY. The effects of cognitive exercise therapy on chronic stroke patients' upper limb functions, activities of daily living and quality of life. *J Phys Ther Sci*. 2015; 27(9): 2787-91. Doi:10.1589/jpts.27.2787
- Almhdawi KA, Mathiowetz VG, White M, delMas RC. Efficacy of occupational therapy task-oriented approach in upper extremity post-stroke rehabilitation. *Occup Ther Int*. 2016; 23(4): 444-56. Doi: 10.1002/oti.1447

- Bai Z, Zhang J, Zhang Z, Shu T, Niu W. Comparison between movement-based and task-based mirror therapies on improving upper limb functions in patients with stroke: A pilot randomized controlled trial. *Fron Neurol*. 2019; 10: 288. Doi: 10.3389/fneur.2019.00288

**It is also unclear whether therapists using the technique are constant in quality.**

**Response:** Thank you very much for pointing it out. The professional therapists, who are in charge of the intervention in the Perfetti Method, will be accredited by the Spanish Association of Cognitive Rehabilitation Perfetti (AERCP). In addition, they must have completed the pertinent training courses corresponding to the two remaining techniques (MT and task-oriented training). We have added in the manuscript some information about it.

P13, lines 2-5: *“To maintain the quality of data collection, the initial evaluation, follow-up, and intervention visits will be conducted by properly trained and accredited therapists, who would follow the standardized methodological criteria mentioned in the data collection manual. Therapists conducting initial and follow-up visits will be different from those who provide different rehabilitation techniques.”*

**Also, there is no specific description of what kind of training patients will be undergoing with Task-Oriented Motor Learning (TOML).**

**Response:** Thank you very much for pointing it out. We have not understood correctly what you mean. If you refer to the training that will be carried out from the task-oriented learning, it is not a specific training. During the intervention, a motor sequence will be carried out aimed at achieving a clear functional objective. This objective may involve complete tasks, such as bringing the fork to the mouth, or it may be the previous movements directed to the entire limb or to a segment, such as grasping the fork.

You can check this information in the following document:

- French B, Forster A, Langhorne P, Leathley MJ, McAdam J, Price CIM et al. Repetitive task training for improving functional ability after stroke. *Cochrane Database Syst Rev*. 2007; 4: CD006073 Doi: 10.1002/14651858.CD006073.pub2

In this protocol, task-oriented training is used in such a way that each day of the week is devoted to a basic activity of daily life (BADL), modifying aspects of the task to increase its difficulty

progressively. The tasks to be trained are feeding (preparing and organizing food, as well as mealtime), clothing (upper and lower extremities) and personal hygiene (brushing teeth, combing hair and shaving or applying makeup), taking into account the patient's preferences, dedicating the last week to the tasks that he/she proposes.

We have added this information to the article, based on the previous reference.

P9, lines 9-15: *“Every day of the week will be dedicated to a different BADL among the following: diet (preparing and organizing food, as well as time taken to eat), clothing (upper and lower extremities), and personal hygiene (brushing teeth, combing hair, and shaving or applying makeup). There will be short resting periods, and the difficulty of tasks will be progressively increased to assist carry over. The last week will be dedicated to tasks and BADL that the patient requests and can be performed at home<sup>50</sup>.”*

50. French B, Forster A, Langhorne P, Leathley MJ, McAdam J, Price CIM et al. Repetitive task training for improving functional ability after stroke. *Cochrane Database Syst Rev.* 2007; 4: CD006073 Doi: 10.1002/14651858.CD006073.pub2

**The function, usage of upper limbs, and cognitive function are well evaluated, but the “compensation strategies” described in the introduction have not been evaluated.**

**Response:** Thank you very much for pointing it out. The assessments used to evaluate movements allow quantifying functional movement (ARAT y Fugl Meyer), the quantity and the quality of use of upper extremities (MAL), the manipulative value of the hand (BBT) and the spasticity of all the movements of the upper extremity (Ashworth), but not compensatory movements. An improvement in components such as joint range, spasticity, quality of use, manipulative skill, etc., leads to a reduction in compensatory strategies. Although, due to the complexity of a complete and quantitative assessment of

compensation strategies, to avoid confusion, the objective has been re-written to: **Abstract:** P2, lines 6-9: *“The objective of this study is to evaluate which of these techniques, MT and CTE, combined with task-oriented training is more effective in functional recovery and movement patterns of the upper extremities in patients with severe hemiparesis after stroke.”*

**Introduction:** P7, lines 11-13: *“Therefore, the objective of this study is to evaluate which of these techniques combined with task-oriented training is more effective in functional recovery and movement patterns of the upper extremities in patients with severe hemiparesis after stroke.”*



## **Response to Reviewer 2**

First of all, we would like to express our sincere gratitude for all comments and suggestions received from the Reviewer 2. This information has certainly enriched the text for its best understanding, thank you very much indeed. We have clarified the reviewer's questions. We have introduced the required changes both in our answers to the specific comments and in the final manuscript.

### **Broad comments:**

**Title:** this appears to be a pilot. It cannot be a definitive trial as no similar trial has preceded it. What about feasibility of delivery, has this been looked at?

**Response:** Thank you very much for pointing it out. We have included the word "pilot" in the title.

**Title:** P1, lines 1-3: *"Effects of home-based mirror therapy and cognitive therapeutic exercise on the improvement of the upper extremity functions in stroke patients with severe hemiparesis: a protocol for a pilot randomized clinical trial."*

**If this is a home-based study, then this should be reflected in the title and abstract.**

**You should also add some literature on home-based upper limb studies.**

**Response:** Thank you very much for pointing it out. We have added new information about the home-based study in the title, abstract and introduction.

**Title:** P1, lines 1-3: *"Effects of home-based mirror therapy and cognitive therapeutic exercise on the improvement of the upper extremity functions in stroke patients with severe hemiparesis: a protocol for a pilot randomized clinical trial."*

**Abstract:** P2, lines 5-6: *"Home-based interventions are an appropriate alternative to promote independence and autonomy."*

**Introduction:**P5, lines 1-10: “Home-based therapy programs for recovery after stroke significantly improve independence and participation in ADL. These programs reduce long-term dependency<sup>16,17</sup> and are at least as effective as hospital interventions<sup>18</sup>. Despite the limited number of studies reporting on specific home-based therapy programs for the functional recovery of the upper extremity following stroke<sup>16,19</sup>, people who receive interventions for improving the functionality and reducing deterioration in the upper extremities have been shown to be more independent and more likely to maintain these skills in the long term if they receive this kind of therapy service<sup>20</sup>. At home, patients are forced to face the real challenges of daily life; therefore, in addition to improving functional outcome and satisfaction<sup>21,22</sup>, this type of intervention reduces depression<sup>23</sup> and encourages motivation and generalization of learning<sup>24,25</sup>.”

We have added these references in the manuscript:

16. Aziz NA, Leonardi-Bee J, Phillips M, Gladman JRF, Legg L, Walker MF. Therapy-based rehabilitation services for patients living at home more than one year after stroke. *Cochrane Database Syst Rev.* 2008; 2: CD005952. Doi: 10.1002/14651858.CD005952.pub2
17. Langhorne P, Baylan S. Early supported discharge services for people with acute stroke. *Cochrane Database Syst Rev.* 2017; 7(7): CD000443. Doi: 10.1002/14651858.CD000443.pub4
18. Roderick P, Low J, Peasgood T, Mullee MA, Turbull JC, Villar T et al. Stroke rehabilitation after hospital discharge: A randomized trial comparing domiciliary and day-hospital care. *Age Ageing.* 2001; 30(4): 303-10. Doi: 10.1093/ageing/30.4.303
19. Coupar F, Pollock A, Legg LA, Sackley C, van Vliet P. Home-based therapy programmes for upper limb functional recovery following stroke. *Cochrane Database Syst Rev.* 2012; 5: CD006755. Doi: 10.1002/14651858.CD006755.pub2
20. Outpatient Service Trialists. Therapy-based rehabilitation services for stroke patients at home. *Cochrane Database Syst Rev.* 2003; 1: CD002925. Doi: 10.1002/14651858.CD002925
21. Minelli C, Gondim F, Antunes Barreira A, Dromerick A. Rehabilitation of the upper extremity and basic activities of daily living in the first month after ischemic stroke: an international cohort comparison study. *Neurol Int.* 2009; 1(1):e4. Doi: 10.4081/ni.2009.e4 22.
22. Gilbertson L, Langhorne P, Walker A, Murray GD. Domiciliary occupational therapy for patients with stroke discharged from hospital: Randomised controlled trial. *BMJ.* 2000; 320(7235): 603-6. Doi: 10.1136/bmj.320.7235.603
23. Chaiyawat P, Kulkantrakorn K, Sritipsukho P. Effectiveness of home rehabilitation for ischemic stroke. *Neurol Int.* 2009; 1(1): 36-40. Doi: 10.4081/ni.2009.e10

24. Björkdahl A, Nilsson ÅL, Grimby G, Sunnerhagen KS. Does a short period of rehabilitation in the home setting facilitate functioning after stroke? A randomized controlled trial. *Clin Rehabil*. 2006; 20(12): 1038-49. Doi: 10.1177/0269215506071230
25. Thorsén AM, Holmqvist LW, de Pedro-Cuesta J, Von Koch L. A randomized controlled trial of early supported discharge and continued rehabilitation at home after stroke: Five-year follow-up of patient outcome. *Stroke*. 2005; 36(2): 297-302. Doi: 10.1161/01.STR.0000152288.42701.a6.

**If this is a study for severe hemiparesis, which it is, then this should be in the title and clearly described in the manuscript. Again, link to the lack of research in this area, cite the relevant papers on severe hemiparesis.**

**Response:** Thank you very much for pointing it out. We have added the word “severe” in the title and new information in the introduction.

**Title:** P1, lines 1-3: “*Effects of home-based mirror therapy and cognitive therapeutic exercise on the improvement of the upper extremity functions in stroke patients with severe hemiparesis: a protocol for a pilot randomized clinical trial.*”

**Introduction:** P4, lines 12-25: “*Severe hemiparesis of the upper extremities, classified according to the Brunnstrom scale between stages II and IV or II and V depending on the author who considers it, is the most frequent cause of functional disability<sup>7</sup>. It is defined as the modification in the ability to perform a normal level of muscular strength, including altered sensitivity, weakness, motor control, and spasticity. It limits the performance of Daily Living Activities (DLA), significantly affecting the quality of life of patients with stroke<sup>8-11</sup>. Studies have shown that functional deficits after stroke are determined by different factors, including the structural extent of the damage and the level of cortical stimulation during the active or passive movement of the affected extremity. This fact must be considered in patients with severe hemiparesis, as first, the motor impairment they present prevents or limits the performance of functionally relevant activities of the affected extremity, and second, severe hemiparesis is commonly accompanied by sensory deficits. Therefore, despite increasing the use of the affected extremity to perform activities in traditional therapies, activation at the cortical level remains very limited<sup>8-11</sup>.*”

We have added this reference in the manuscript:

10. Hara T, Abo M, Kakita K, Masuda T, Yamazaki R. Does a combined intervention program of repetitive transcranial magnetic stimulation and intensive occupational therapy affect

cognitive function in patients with post-stroke upper limb hemiparesis? *Neural Regen Res.* 2016; 11(12): 1932-9. Doi: 10.4103/1673-5374.197134

**Discussion:** P15, lines 14-21: “Vandana et al.<sup>48</sup> evaluated the effects of MT on motor recovery of the upper extremities, spasticity, and hand-related functionality of patients with subacute stroke and severe hemiparesis (stages II to IV of the Brunnstrom scale). Moreover, a greater improvement in the scores of the Brunnstrom stages for the hand and upper extremity was observed in the MT group than the conventional therapy group. Ayra et al.<sup>63</sup> evaluated a specific task-based neurorehabilitation therapy among patients with subacute stroke with severe hemiparesis (stages II to V of the Brunnstrom scale) and showed that there were greater improvements in performing activities with this method than with any other conventional method.”

We have added this reference:

63. Arya KN, Verma R, Garg RK, Sharma VP, Aggarwal M, Aggarwal GG. Meaningful task-specific training (MTST) for stroke rehabilitation: A randomized controlled trial. *Top Stroke Rehabil.* 2012; 19(3): 193-211. Doi: 10.1310/tsr1903-193

**Please clarify that this is a single blinded, three armed parallel study and be consistent with this throughout.**

**Response:** Thank you very much for pointing it out. We have clarified these terms throughout the manuscript.

**Abstract:** P2, lines 11-12: “This is a home-based, single-blind, controlled, randomized clinical trial with three parallel arms...”

**Methods and analysis:** P7, lines 18-19: “This is a single-blinded, controlled, randomized clinical trial with three parallel arms (control, intervention 1, and intervention 2)...”

**The inclusion criteria are quite open.**

**Response:** Thank you very much for pointing it out. The main criteria to be able to take part of the study is to have severe hemiparesis, considering the Brunnstrom Scale, excluding all people with cognitive impairment, heminegligence, Wernicke's or mixed aphasia, and homonymous

hemianopsia. These criteria have been determined due to people with these characteristics cannot perform the proposed interventions based on mirror therapy or cognitive therapeutic exercise, combined with the task-oriented training.

**If there are subtle changes in UL function how will you measure these, the Fugl and ARAT may not detect anything? Secondary (cognitive) measures may show change.**

**Response:** Thank you very much for pointing it out. The Fugl Meyer is one of the most widely used assessments to evaluate upper extremities after a stroke (in 36% of studies) with good psychometric properties, sensitive enough to detect subtle changes, but for a thorough assessment it must be combined with other functional measures. Therefore, this study combines the Fugl Meyer with the ARAT and the MAL (another two of the most used assessments) and the BBT. These scales evaluate the functionality of the upper extremity, which is not a criteria to be able to take part of the study. The main criteria is to have severe hemiparesis, considering the Brunnstrom Scale, excluding all people with cognitive impairment, heminegligence, Wernicke's or mixed aphasia, and homonymous hemianopsia. These people will be excluded because they will not be able to carry out interventions based on MT or ETC, combined with the task-oriented training. This information is based on this reference:

- Santisteban L, Térémetz M, Bleton JP, Baron JC, Maier MA, Lindberg PG. Upper limb outcome measures used in stroke rehabilitation studies: A systematic literature review. *PLoS One*. 2016; 11(5): 1-16. Doi: 10.1371/journal.pone.0154792

**How are you screening for Aphasia, what is the threshold for exclusion?**

**Response:** Thank you very much for pointing it out. We have indicated how the exclusion criteria will be assessed. Only patients with Broca's aphasia could be included in the study. Taking into account the diagnostic criteria of the neurology service professionals, patients with Wernicke's aphasia and mixed aphasia will be excluded from the study.

P8, lines 3-5: "Participants presenting hemineglect, Wernicke's aphasia, mixed aphasia, and/or visual deficits (homonymous hemianopsia) will be excluded from the study, considering the diagnostic information provided by the clinical assessment of neurologist."

**Sample size is stated, yet you describe how the power calculation will be performed.**

**Response:** Thank you very much for pointing it out.

P8, lines 17-23: *“The sample size has been estimated on the basis of the potential modification of the main variable, i.e., the functionality of the affected upper extremity. Given alpha and beta risks of 0.05 and 0.20, respectively, in bilateral contrast, 110 participants (55 per group) will be required to detect a minimum difference of 0.50 in the functionality of the affected upper extremity using the Fugl-Meyer Assessment (FMA) between the two groups. An additional 44 individuals will be needed for calculating the size of the spontaneous improvement group, which is estimated to occur in 20% of the cases<sup>48</sup>. A predicted dropout rate of 10% during follow-up has been considered.*

**Make the research question clear throughout the manuscript**

**Response:** Thank you very much for pointing it out. We have re-made the research question.

**Introduction:** P5, lines 11-15: *“This study is designed to create a home-based therapy program for the functional recovery of the upper extremities using mirror therapy (MT) or cognitive therapeutic exercise (CTE) in combination with task-oriented training and to verify which of these two techniques is more effective in functional recovery and movement patterns of the upper extremities in patients with severe hemiparesis after a stroke.”*

**Clearly state the primary outcome measure and primary end-point (for example Fugl Meyer, week 13). In the abstract and methodology.**

**Response:** Thank you very much for pointing it out. The primary outcome will be measure by the Fugl-Meyer scale, which will be combined with other scales (ARAT, MAL, BBT and Ashworth) in order to achieve a thorough assessment. The primary and secondary end-point will be evaluated at 6 months post-stroke. We have introduced the required information in the abstract and methodology.

**Abstract:** P2, lines 12-14: *“The primary outcome will be the functionality of the affected upper extremity measured using the Fugl-Meyer assessment”*

**Methods and analysis:**

P11, lines 25-28: *“The primary outcome will be an improvement in the functionality of the affected upper extremity. The secondary variables will include cognitive performance, emotional state, quality of life, and performance of ADL. The primary and secondary endpoints will be evaluated at six months poststroke through the use of questionnaires, previously validated for the Spanish population.”*

P11, lines 30-31: *To perform a thorough assessment, different motor deficit components of the affected upper extremity will be evaluated using the FMA, which will be combined with four other scales.”*

**Clearly describe the statistical analysis for the primary outcome data, t-test, ANOVA?  
Currently this is quite unclear.**

**Response:** Thank you very much for pointing it out. We have re-written the statistical

analysis section; in order to clarify it

P13, lines 23-33; P14, lines 1-18:

*“General Analysis*

*The results of the main and the secondary variables will be analyzed using intention-to-treat (ITT) analysis to control the effects of nonrandom abandonment. The mean and standard deviation will be used for the description of the quantitative variables or frequency distribution and percentages for categorical variables. The normality of the variables will be assessed using the Kolmogorov-Smirnov test. In cases where the normal distribution cannot be assumed, median, interquartile range, and the corresponding nonparametric test will be used. The association between independent categorical variables will be analyzed using  $\chi^2$  test or Fisher’s exact test. The means between the two groups will be compared using the Student’s t-test or the Mann-Whitney U-test. Pearson’s or Spearman’s correlation coefficients will be calculated to analyze the relationship between quantitative variables. A p-value of <0.05 was considered statistically significant. The statistical analysis will be performed using the SPSS software version 25.0 (IBM SOSS Inc, Chicago, IL, USA).*

*Analysis of the effects of the intervention on primary and secondary outcomes*

*To analyze the changes at six weeks and six months from baseline in the primary (functionality of the affected upper extremity) and secondary outcomes within the same group, the Student's t-test for paired data or Wilcoxon test will be used.*

*The effects of the intervention will be analyzed by comparing the changes in the functionality of the affected upper extremity between groups using the analysis of covariance of change score, with the baseline as covariate and by adjusting for possible confounders. The effects of the intervention during follow-up will be studied using an analysis of the variance of repeated measures.*

#### *Analysis by subgroups*

*The effects of the intervention can be influenced by age, sex, type of stroke, affected cerebral hemisphere, and stroke severity. The same analysis described above will be performed for each of the subgroups.*

#### *Secondary analysis*

*A multivariate multiple regression analysis will be performed to identify the variables that greatly influence the changes in the functionality of the affected upper extremity and the secondary variables analyzed.”*

**Be consistent with terms (BDLA, DLA, ADL).**

**Response:** Thank you very much for pointing it out. We have replaced the acronym of daily life activities throughout the manuscript.

**There doesn't appear to be a Cochrane review of UL RCTs. This, and the recommendations it contains must be cited (Poolock et al, 2013). You will find this and one for home-based interventions (I think) in the Cochrane library database.**



**Response:** Thank you very much for pointing it out. We have added new information and bibliography founded in the Cochrane library database related to home-based interventions and upper limb interventions following stroke. This information has been explained in a previous point.

**P. 3, line 17: Your inclusion criteria don't really reflect this. They may have no movement at all according to the Brunnstrom scores you've given. Could you say 'severe' hemiparesis, or 'severe hemiparesis showing early signs of movement'?**

**Response:** Thank you very much for pointing it out. We have introduced the required changes.

P2, lines 3-5: *"Mirror therapy (MT) and cognitive therapeutic exercise (CTE) are two neurorehabilitation techniques based on neuroplasticity and designed to improve the motor functions of the affected upper extremity in patients with severe hemiparesis after stroke.*

**P. 3, line 35: this isn't needed.**

**Response:** Thank you very much for pointing it out. This information has been removed from the manuscript.

**P. 4, lines 5-8: Do the authors mean that if this trial is successful, patients will be able to self deliver all interventions? Please clarify.**

**Response:** Thank you very much for pointing it out. We have reformulated the phrase to clarify its meaning

P3, lines 3-4: *"This study will use stroke-related neurorehabilitation techniques, which would enable an easy at-home application to the patient."*

**P. 4, lines 9-12: Not really a strength, this is a necessity.**

**Response:** Thank you very much for pointing it out. We have removed the comment and added a new strength from the study.

P3, lines 5-7: *“The sample size will provide greater confidence and credibility regarding the benefits of these neurorehabilitation approaches and help in understanding the relevant aspects to conduct future studies”*

**P. 4, lines 13-16: You mean that this is a single-blinded trial.**

**Response:** Thank you very much for pointing it out. We have re-written this sentences in order to clarify its meaning.

P3, lines 8-9: *“Because of the nature of the intervention, the participants will not be blinded; however, the researchers who perform the measurements and statistical analysis will be blinded.”*

**P. 4, line 31: after dementia? not known for being cause of physical disability primarily.**

**Response:** Thank you very much for pointing it out. We have re-written this sentence, deleting the information about dementia.

P4, lines 5-6: *“Stroke requires urgent neurological assistance and is the principal cause of physical disability among adults<sup>2</sup>”.*

**P. 5, line 30-31: In the context of a RCT? Perhaps re-word this. Was there any clinical significance? How have you changed your delivery based on their findings? This statement may indicate that the researchers are not in a position of equipoise. Response:** Thank you very much for pointing it out. We have introduced the required changes.

P5, lines 26-28: *“However, Oliveira and Castro<sup>35</sup> did not observe considerable improvements in self care because of different limitations such as the short duration of the program, small sample size, and lack of randomization.”*

**P. 5, line 43-44: Since tactile feedback has been highlighted in some guidelines as an essential part of UL rehab and is impaired in about 60% of those with UL hemi, there should be some mention of what the tactile.**

**Response:** Thank you very much for pointing it out. We have added some information about tactile feedback in the manuscript.

P6, lines 3-9: *“The proprioceptive information received is associated with the recognition of the direction, distance, and shapes through the body. The information associated with touch refers to the recognition of characteristics that are deduced by touching the object. The problem raised while perceiving the information can only be solved if the nature, intensity, and characteristics of the contact made are recognized. Therefore, the exercises are based on what the patient needs to recognize in an object: surface, pressure, friction resistance, or weight<sup>36</sup>.”*

We have added a new reference:

36. Perfetti C, Ghedina R, Jiménez Hernández D. El ejercicio terapéutico cognoscitivo para la reeducación motora del hemipléjico adulto. Barcelona: Edika Med; 1999.

**P. 5, line 60: Reported as...**

**Response:** Thank you very much for pointing it out. We have introduced the required changes in the manuscript.

P6, line 18: *“However, despite the fact that it is reported as one of the most complete and effective methods for the rehabilitation of neurological deficit in the upper extremities<sup>38</sup>, new studies with a larger sample size are warranted, which could define aspects such as time and materials required for their implementation<sup>37-39</sup>.”*

**P. 6, line 3: I don't think you can really translate or interpret research and literature into this. Stroke is heterogeneous by it's nature. The inclusion criteria for this proposed study is extremely broad.**

**Response:** Thank you very much for pointing it out. You are right about the heterogeneity of the stroke, so we have removed the concept of homogeneity in this sentence.

P6, lines 18-21: *“However, despite the fact that it is reported as one of the most complete and effective methods for the rehabilitation of neurological deficit in the upper extremities<sup>38</sup>, new studies with a larger sample size are warranted, which could define aspects such as time and materials required for their implementation<sup>37-39</sup>.”*

**P. 6, line 51: Your Brunstrom inclusion criteria doesn't clearly reflect this.**

**Response:** Thank you very much for pointing it out. We want to say severe hemiparesis instead residual, so we have changed the term "residual" to "severe" in this sentence and throughout the manuscript.

**P. 7, line 11: 154 participants recruited in 18 months!?**

**Response:** Thank you very much for pointing it out. We will be recruiting patients for a period of 18 months or until such time as the required sample size is reached

**P. 7, lines 11-12: Can this be written as: baseline, 6 wks (post-intervention) (why two visits?), Wk 13 (three-month follow-up?), why week 13? Often the follow up is at 6 months.**

**Response:** Thank you very much for pointing it out. We have specified the duration of the intervention, according to the review recommendations.

*P7, lines 20-24: "At the first visit, just one month after having suffered from stroke, patients will be determined to meet the inclusion criteria, and the initial evaluation will be performed for patients who meet the criteria. A postintervention visit after six weeks will be conducted, and a follow-up visit will be conducted six months after stroke to evaluate the progress of patients in the subacute phase of recovery."*

**P. 7, line 16: Recruited whilst on the unit. Commence the trial once discharged? There can be great variability in time post-stroke discharge. For example some patients may be in-patients for 6 months+ because of other complications, meanwhile their arm recovers. This presents the potential for unequal groups, and this requires stratified recruitment. Or, this means that the patient may be outside of the inclusion by the time of discharge. Authors need to clarify if 'participants will be recruited at point of discharge.**

**Response:** Thank you very much for pointing it out. Although the patients are recruited during their hospital stay, just before the first evaluation and the intervention it will be verified that they meet the inclusion criteria, especially the one related to the state of the upper limb (Brunnstrom),

because it can change a lot during the first month after the stroke. During hospital recruitment, the inclusion criteria related to the Brunnstrom scale will not be given much importance since this period is usually related to the first stage (flaccidity, hypotonia, absence of voluntary movements, etc.), but one month later the status of the upper limb may be very different. The intervention begins just one month after having suffered the stroke. At this stage, often called subacute, it is likely that patients are between stages II and IV of the Brunnstrom scale, one of the main inclusion criteria in this study.

You can check the information in the following article:

- Vandana, MP, Patitapaban M. Effectiveness of mirror therapy in rehabilitation of hand function in sub-acute stroke. *Palliat Med Care*. 2017; 4(2): 1-8. Doi: 10.15226/2374-8362/4/2/00135

We have added some information to clarify it:

*P7, lines 20-22: "At the first visit, just one month after having suffered from stroke, patients will be determined to meet the inclusion criteria, and the initial evaluation will be performed for patients who meet the criteria."*

**P. 7, lines 23-27: Necessarily broad as recruitment can be challenging and the numbers aimed for here in order to attain greater significance/confidence require this breadth. Time since stroke?**

**Response:** Thank you very much for pointing it out. Although the recruitment will be done during the hospital stay, one month after the stroke it will be verified that the selected patients meet the inclusion criteria. Therefore, the time since the stroke will be one month.

**P. 7, lines 39-41: Why? Due to previous feasibility design with PPI? Because these interventions can be part of usual care? Using PPI to demonstrate exercises and obtain feedback on patient experience and tolerance, particularly the slow movemetn frequecny described here later and the modal approach, surely is necessary. It can be incredibly frustrating.**

**Response:** Thank you very much for pointing it out. We have introduced the required changes.

P8, lines 17-23: *“The patients and the public will participate in the study design so that time and spaces necessary for the home-based intervention could be adapted according to their availability. Moreover, they will be part of the data collection process and will be informed of the results obtained. Participants may suggest changes related to the frequency and intensity of the sessions.”*

**P. 7, lines 50-52: Has been estimated? In the abstract n=154 is stated.**

**Response:** Thank you very much for pointing it out. We have rewritten this sentence, taking into account your previous indications

P8, lines 17-18: *“The sample size has been estimated on the basis of the potential modification of the main variable, i.e., the functionality of the affected upper extremity.”*

**P. 8 line 7: Estimated, not ‘bound to’.**

**Response:** Thank you very much for pointing it out. We have rewritten this sentence, taking into account your previous indications

P8, lines 18-23: *“Given alpha and beta risks of 0.05 and 0.20, respectively, in bilateral contrast, 110 participants (55 per group) will be required to detect a minimum difference of 0.50 in the functionality of the affected upper extremity using the Fugl-Meyer Assessment (FMA) between the two groups. An additional 44 individuals will be needed for calculating the size of the spontaneous improvement group, which is estimated to occur in 20% of the cases<sup>48</sup>. A predicted dropout rate of 10% during follow-up has been considered.”*

**P. 8 line 20: Where does this sentence belong? What is it refer to?**

**Response:** Thank you very much for pointing it out. We have re-written the sentence in order to clarify its meaning

P8, lines 31-32: *“The standard rehabilitation treatment for stroke will be used for all study participants. Participants included in the CG will not receive any additional treatment or therapy”*

**P. 8 line 27: So this is home-based?**

**Response:** Thank you very much for pointing it out. It is, we have clarified that it is a home-based intervention throughout all manuscript

**P. 8 line 27: so daily for 5 days per-week, making 30 clinical contacts? Is there a rationale for this dosage? The question must be asked. since so much has been published regarding the importance of dosage for UL rehab.**

**Response:** Thank you very much for pointing it out. There is no specific recommended dose to carry out these therapies and achieve greater recovery. The therapy has to be intensive enough to achieve significant changes in functional improvement. Therefore, this dose has been based on previous studies that have achieved significant improvements in the functionality of the upper limb with severe hemiparesis, carried out in the same type of population. You can check the information in the following articles:

- Radajewska A, Opara JA, Kucio C, Błaszczyszyn M, Mehlich K, Szczygiel J. The effects of mirror therapy on arm and hand function in subacute stroke in patients. *Int J Rehabil Res.* 2013; 36(3): 268-74. Doi: 10.1097 / MRR.0b013e3283606218
- Almhdawi KA, Mathiowetz VG, White M, del Mas RC. Efficacy of occupational therapy task-oriented approach in upper extremity post-stroke rehabilitation. *Occup Ther Int.* 2016; 23(4): 444-56. Doi: 10.1002 / oti.1447.
- Bai Z, Zhang J, Zhang Z, Shu T, Niu W. Comparison between movement-based and task-based mirror therapies on improving upper limb functions in patients with stroke: A pilot randomized controlled trial. *Front Neurol.* 2019; 10: 288. Doi: 10.3389 / fneur. 2019.00288

**P. 8 line 40: So this is to assist carry-over.**

**Response:** Thank you very much for pointing it out. We were referring to “assist carry-over”, so we have added the concept.

P9 lines 9-13: *“Every day of the week will be dedicated to a different BADL among the following: diet (preparing and organizing food, as well as time taken to eat), clothing (upper and lower extremities), and personal hygiene (brushing teeth, combing hair, and shaving or applying makeup). There will be short resting periods, and the difficulty of tasks will be progressively increased to assist carry-over”*

**P. 8 line 50: I would say 'hand' not member, for consistency.**

**Response:** Thank you very much for pointing it out. We have replaced "member" for "extremity". The MT involves the entire affected extremity, and not just the hand.

P9, lines 18-20: *"The affected extremity must be placed behind the mirror, in a comfortable position, in such a way that the patient cannot see it."*

**P. 9, line 12-14: How will movement frequency be regulated? What is the rationale for the 15 reps? Seems a low number.**

**Response:** Thank you very much for pointing it out. The number of repetitions that the exercise must be performed from the Mirror Therapy is at least 15 times to achieve optimal results, according to the protocol of practice for the rehabilitation of the stroke from the Mirror Therapy. You can check the information in the following protocol:

- Rothgangel AS, Braun SM. 2013. Mirror therapy: Practical protocol for stroke rehabilitation.

Munich: Pflaum Verlag. Doi: 10.12855/ar.sb.mirrortherapy.e2013

**P. 9, lines 28-30: Usually described as reducing or minimising compensatory.**

**Response:** Thank you very much for pointing it out. The terminology used has been "abnormal irradiation" (involuntary activation of muscle groups), because that is how it is called from the Perfetti Neurorehabilitation Method that has been used. It focuses on the recovery of the most elemental components of the stroke patient's specific deficit identified as: abnormal reactions to stretching, abnormal irradiations, elementary schemes and alteration of motor recruitment.

You can check this information in the following articles:

- Sallés L, Gironès X, Martín-Casas P, Lafuente JV. A neurocognitive approach to recovery of movement following stroke. *Physical Therapy Reviews*. 2015;20(5-6): 283-289. doi.org/10.1080/10833196.2015.1111579



- Sallés L, Martín-Casas P, Gironès X, Durà MJ, et al. A neurocognitive approach for recovering upper extremity movement following subacute stroke: a randomized controlled pilot study. *Journal of Physical Therapy Science*. 2017;29(4): 665-672. doi.org/10.1589/jpts.29.665
- Perfetti C, Ghedina R, Jiménez Hernández, D. El ejercicio terapéutico cognoscitivo para la recuperación motora del hemipléjico adulto. 1998. Barcelona: Edika-Med

**P. 9, lines 45-47: This all supports the need for bespoke support based on individual patient needs and progress. The modal approach needs to be clarified a bit in terms of how much is experimental and how much directly derived from any published recommendations. Just so long as this is clear.**

**Response:** Thank you very much for pointing it out. We have introduced the required changes.

P10, 9-19: *All patients will begin performing the first-grade exercises until they regain the ability to control the reaction to stretching to graduate intensity, time, and spatiality. Once the patient can successfully perform the first-degree exercises, control the reactions to stretching in a sufficiently automated way, and frequently perform selective movements of the fingers and other body segments, the second-degree exercises are performed<sup>39,53</sup>. Finally, third-degree exercises are performed through which the patient learns to adapt movements to the proposed perceptual hypothesis after the patient has managed to automate the control of abnormal motor behaviors with the second-degree exercises. The criteria that must be considered to establish correct programming of the exercises depend on the configuration of the trajectories that are requested from the patient and on the intensity of the contractions that must be activated in the segments that execute them<sup>36</sup>*

We have added these new references:

36. Perfetti C, Ghedina R, Jiménez Hernández D. El ejercicio terapéutico cognoscitivo para la reeducación motora del hemipléjico adulto. Barcelona: Edika Med; 1999.
39. Sallés L, Martín-Casas P, Gironès X, Durà MJ, Lafuente JV, Perfetti C. A neurocognitive approach for recovering upper extremity movement following subacute stroke: A randomized controlled pilot study. *J Phys Ther Sci*. 2017; 29(4): 665-72. Doi: 10.1589 / jpts.29.665
53. Sallés L, Gironès X, Martín-Casas P, Lafuente JV. A neurocognitive approach to recovery of movement following stroke. *Phys Ther Rev*. 2015; 20(5-6): 283-9. Doi: 10.1080/10833196.2015.1111579

**P. 11, lines 48-54: Can some clarity be added here: all interventions will be delivered by the researcher (PI). Data will be collected by research assistants blind to participant allocation? In which case it is single blinded? Can the authors confirm.**

**Response:** Thank you very much for pointing it out. We have introduced the required changes.

P13, lines 15-20: *“This is a single-blinded study. Because of the nature of the intervention, the participants and people responsible for using the MT or CTE, both combined with task-oriented training, to IG cannot be blinded. However, the person taking the measurements during the follow-up visit and the researcher analyzing the data statistically will be blinded with respect to the group to which the participants belong. In addition, clear instructions will be provided to the participants of not revealing the group to which they have been assigned during the assessment visits.”*

### **Response to Reviewer 3**

First of all, we would like to express our sincere gratitude for all comments and suggestions received from the Reviewer 3. This information has certainly enriched the text for its best understanding, thank you very much indeed. We have clarified the reviewer’s questions. We have introduced the required changes both in our answers to the specific comments and in the final manuscript.

### **Broad comments:**

**The International Classification of Functioning (ICF) could also be useful to describe the primary and secondary outcome of interests. For example, upper limb function at both the body function/structure and the activity levels should be the primary outcome measure, instead of the “upper limb functionality”.**

**Response:** Thank you very much for pointing it out. We have changed the primary outcome, according to your indications

**P.3, lines 17-19: The objective of this study should be clearly spelled out.**

**Response:** Thank you very much for pointing it out. We have re-write the objective, following yours recommendations.

P2, lines 7-9: *“The objective of this study is to evaluate which of these techniques, MT and CTE, combined with task-oriented training is more effective in functional recovery and movement patterns of the upper extremities in patients with severe hemiparesis after stroke.”*

**P.3, lines 26-28: The acronym for daily life activities (DAL) should be replaced by ADL (activities of daily living) – a term that is more commonly used in rehabilitation.**

**Response:** Thank you very much for pointing it out. We have replaced the acronym of daily life activities throughout the manuscript.

**P.3, lines 28-29: It is unclear what the 3 intervention groups are. Please clarify that the study involves 2 intervention groups (mirror therapy + task-oriented motor learning and cognitive therapeutic exercises + task-oriented motor learning) and 1 control group.**

**Response:** Thank you very much for pointing it out. We have clarified the required information about interventions groups.

P2, lines 15-17: *“During six weeks, one of the intervention groups will receive a treatment based on MT and the other one on CTE, both combined with task-oriented training. No additional interventions will be provided to the control group.”*

**P.3, lines 31-33: Please specify the duration of the intervention. Maybe the first follow-up visit should be replaced by the term “post-intervention”, with the term “follow-up” could be used to describe the last follow-up visit done at week 13.**

**Response:** Thank you very much for pointing it out. We have specified the duration of the intervention, according to the review recommendations.

P2, lines 17-20: “To assess the progress of patients with stroke in the subacute phase, all variables will be evaluated at different visits: initial (just before starting treatment and four weeks poststroke), postintervention (six weeks after initial), and follow-up (six months).”.

**P.3, line 47: The expected contributions from this work are missing (if the authors are lacking space, the ethical portion could be shortened).**

**Response:** Thank you very much for pointing it out. We have added the expected contributions from this work.

P2, lines 27-29: *“These study results will provide relevant and novel information on effective neurorehabilitation strategies and improve the quality of intervention programs aimed at patients after stroke.”*

**P.4, line 53-59: The stroke recovery process described here is inexact. Spontaneous recovery can continue to occur even after 1 month post-stroke, while experience-dependent recovery (also called plasticity) can occur immediately after stroke and throughout the rehabilitation process. There is a vast body of literature related to stroke recovery.**

**Response:** Thank you very much for pointing it out. The intervention starts after one month of the stroke because it is intended to act in a subacute stage. The chosen therapies are especially effective from this period, because both require complex cognitive processes, which are difficult to activate in the acute stage. Regarding spontaneous recovery, it can occur in later stages, therefore, to determine which results are produced by the intervention and which by spontaneous recovery; a control group has been included in the study.

**P.5, line 7-10: The organization of the introduction does not allow the reader to understand why it is of interest to use Mirror Therapy and Cognitive Therapeutic Exercise. It is also unclear why both interventions are combined with task-oriented motor learning. Moreover, is TOML the same as task-oriented training, a common approach in stroke rehabilitation?**

**Response:** Thank you very much for pointing it out. Mirror Therapy and Cognitive Therapeutic Exercise are two effective methods to recover the mobility of the affected upper extremity. However, the implementation of these therapies along with others that provide a more functional approach, such as task-oriented training, facilitates the generalization of the movements

previously learned to the activities of daily life. Therefore task-oriented training is combined with the other two techniques in order to achieve a greater improvement in functionality.

Effectively, "TOML" is the same as task-oriented training. To avoid confusion, the abbreviations "TOML" have been replaced in the text by "task-oriented training"

**P.5, line 28-31: From reading this sentence, I am questioning why mirror therapy is used in the current study, since previous work has shown that this intervention is not effective. Consider rephrasing this sentence to better nuance why mirror therapy is promising and the factors that may have contributed to the limited effectiveness.**

**Response:** Thank you very much for pointing it out. We have rephrased this sentences to clarify its meaning.

P5, line 26-28: *“However, Oliveira and Castro<sup>35</sup> did not observe considerable improvements in self care because of different limitations such as the short duration of the program, small sample size, and lack of randomization.”*

**P.6, line 42-54: Consider rephrasing the study objective in a PICO (person, intervention, comparison, outcome and time) format. Also, study hypotheses should be presented with appropriate reference to the literature to support each hypothesis.**

**Response:** Thank you very much for pointing it out. We have rephrased the study objective in a PICO format

P7, lines 11-13: *“Therefore, the objective of this study is to evaluate which of these techniques combined with task-oriented training is more effective in functional recovery and movement patterns of the upper extremities in patients with severe hemiparesis after stroke.”*

**P.7, line 21: Unclear what this sentence means. Consider rephrasing.**

**Response:** Thank you very much for pointing it out. We have rephrased this sentence.

P7, line 29-30: All evaluation and follow-up visits and the development of the interventions will be carried out in the patient's home."

**P.7, line 34: Please indicate how the exclusion criteria will be assessed (chart review, clinical assessments, etc.).**

**Response:** Thank you very much for pointing it out. We have indicated how the exclusion criteria will be assessed.

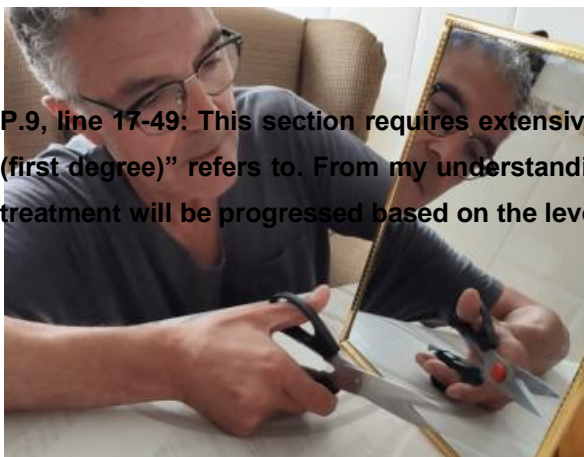
P8, lines 3-5: *"Participants presenting hemineglect, Wernicke's aphasia, mixed aphasia, and/or visual deficits (homonymous hemianopsia) will be excluded from the study, considering the diagnostic information provided by the clinical assessment of neurologist."*

**P.8, line 18: The interventions are described very broadly. It is difficult to assess what will be done during each intervention and whether participants are able to continue to receive their usual care (if what, what is part of the usual care). Understanding the key components of each proposed intervention are needed to allow the reader to understand how neuroplasticity will be targeted by each intervention.**

**Response:** Thank you very much for pointing it out. We have modified the whole Intervention section to make it clearer and we have added some new references. Please, you can check these changes in that section (P9, lines 31-32; P10, lines 1-33; P11, lines 1-32; P12, lines 1-13)

**P. 8, line 48: Consider using a picture of the experimental set-up to facilitate the understanding.**

**Response:** Thank you very much for pointing it out. We included a picture of the experimental set-up



**P.9, line 17-49: This section requires extensive editing. I don't know what "first modality (first degree)" refers to. From my understanding, the authors are trying to describe how treatment will be progressed based on the level of motor impairments of the participants.**

**The description of how treatment will be delivered for individuals with more severe motor impairments is vague (focus on decreasing spasticity by doing passive stretches? If I am correct, how is this still considered task-oriented training?).**

**Response:** Thank you very much for pointing it out. We have modified the whole Intervention section to make it clearer and we have added some new references. Please, you can check these changes in that section (P9, lines 31-32; P10, lines 1-33; P11, lines 1-32; P12, lines 1-13)

**P.9, lines 50-52: Are all participants recruited at stroke onset? The follow-up visit is once post-intervention and then 2 months later? I understand that the recruitment for this study is already underway, but would it be possible to do the follow-up visit at 6 months post-stroke (or 6 months after the initial recruitment to this study) to better understand the progress in individuals beyond the subacute phase of recovery?**

**Response:** Thank you very much for pointing it out. In this study, the participants will be recruited at point of discharge from the Neurological Service and Stroke Unit of the Burgos University Hospital (Spain), by means of consecutive sampling. At the first visit, just one month after having suffered the stroke, it will be determined if they meet the inclusion criteria and, in that case, the initial evaluation will be carried out. The follow-up visits will take place once the intervention has finished and 13 weeks later. We agree with the reviewer's comment that it is better to make the follow-up visit at 6 months to understand the progress of the stroke patients in the subacute phase. We have changed the text in these terms.

P11, lines 17-18: *"A follow-up visit will occur six months poststroke to evaluate the progress of patients with stroke in the subacute phase of recovery."*

**P.10, line 34: Please specify for which joint and which motion (e.g. elbow flexion). Why did you choose the Ashworth scale over the modified Ashworth scale? Response:** Thank you very much for pointing it out. There has been an error in the transcription of the scale; we wanted to refer to the modified Ashworth scales. We have corrected this error in the paragraph.

P12, lines 5-10: *"The Modified Ashworth Scale (55)<sup>58</sup>, which measures the spasticity of all the movements of the different joints of the upper extremity: shoulder (flexion, extension, abduction, adduction, and internal and external rotation); elbow (flexion, extension, pronation, and supination); wrist (flexion, extension, and ulnar and radial deviation); distal and proximal metacarpophalangeal and interphalangeal (flexion and extension); the second to fifth fingers (abduction and adduction); and thumb (flexion, extension, abduction, and adduction)."*

**P.11, line 44: I am unsure if the assessors are blind or not. Having a blind assessor would make this study stronger.**

**Response:** Thank you very much for pointing it out. We have re-written this paragraph in order to clarify this aspect.

P.13, lines 15-20: *“This is a single-blinded study. Because of the nature of the intervention, the participants and people responsible for using the MT or CTE, both combined with task-oriented training, to IG cannot be blinded. However, the person taking the measurements during the follow-up visit and the researcher analyzing the data statistically will be blinded with respect to the group to which the participants belong. In addition, clear instructions will be provided to the participants of not revealing the group to which they have been assigned during the assessment visits.”*

**P.12, line 3: It is unclear if subgroup analyses will be performed. If this is anticipated, the plan to carry out a subgroup analysis should be provided. Response:** Thank you very much for pointing it out. We have re-written the statistical analysis section; in order to clarify it

P13, lines 23-33; P14, lines 1-18:

#### *“General Analysis*

*The results of the main and the secondary variables will be analyzed using intention-to-treat (ITT) analysis to control the effects of nonrandom abandonment. The mean and standard deviation will be used for the description of the quantitative variables or frequency distribution and percentages for categorical variables. The normality of the variables will be assessed using the Kolmogorov-Smirnov test. In cases where the normal distribution cannot be assumed, median, interquartile range, and the corresponding nonparametric test will be used. The association between independent categorical variables will be analyzed using  $\chi^2$  test or Fisher’s exact test. The means between the two groups will be compared using the Student’s t-test or the Mann-Whitney U-test. Pearson’s or Spearman’s correlation coefficients will be calculated to analyze the relationship between quantitative variables. A p-value of <0.05 was considered statistically significant. The statistical analysis will be performed using the SPSS software version 25.0 (IBM SOSS Inc, Chicago, IL, USA).*

*Analysis of the effects of the intervention on primary and secondary outcomes*



*To analyze the changes at six weeks and six months from baseline in the primary (functionality of the affected upper extremity) and secondary outcomes within the same group, the Student's t-test for paired data or Wilcoxon test will be used.*

*The effects of the intervention will be analyzed by comparing the changes in the functionality of the affected upper extremity between groups using the analysis of covariance of change score, with the baseline as covariate and by adjusting for possible confounders. The effects of the intervention during follow-up will be studied using an analysis of the variance of repeated measures.*

#### *Analysis by subgroups*

*The effects of the intervention can be influenced by age, sex, type of stroke, affected cerebral hemisphere, and stroke severity. The same analysis described above will be performed for each of the subgroups.*

#### *Secondary analysis*

*A multivariate multiple regression analysis will be performed to identify the variables that greatly influence the changes in the functionality of the affected upper extremity and the secondary variables analyzed.”*

**P.12, line 12: The word “qualitative” is misleading, since all outcome measures collected are quantitative in nature.**

**Response:** Thank you very much for pointing it out. We have replaced the word “qualitative” by “categorical” in the text, as you can see in the previous point.

P13, lines 25-27: *“The mean and standard deviation will be used for the description of the quantitative variables or frequency distribution and percentages for categorical variables.”*

P13, lines 29-30: *“The association between independent categorical variables will be analyzed using  $\chi^2$  test or Fisher's exact test.”*

**The discussion should also be expanded to better describe what are the expected contributions from this work (aside from publishing the results), what knowledge will be gained by this study and the limitations.**

**Response:** Thank you very much for pointing it out. We have added some new information related to the contributions from this work.

P16, lines 7-22: *“This study will provide novel and useful results for the development of poststroke rehabilitation strategies. The intervention may provide implications for the preparation of evidence-based recommendations, practical clinical guidelines, and continuous quality improvement programs for patients with severe hemiparesis after stroke. The relevant information will be obtained about the functionality of the upper extremity of patients with severe hemiparesis after the practice of a more intensive therapy that combines two types of neurorehabilitation approaches. The sample size of Analysis by subgroups*

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