

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## Effects of Mirror Therapy and Cognitive Therapeutic Exercise on the improvement of the upper extremity functions in stroke patients: a randomized clinical trial protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035768
Article Type:	Protocol
Date Submitted by the Author:	15-Nov-2019
Complete List of Authors:	Gonzalez Santos, Josefa; University of Burgos, Health Sciences Soto-Camara, Raul; University of Burgos, Health Sciences Rodriguez-Fernández, Paula; University of Burgos, Health Sciences Jimenez-Barrios, Maria; University of Burgos, Health Sciences Gonzalez-Bernal, Jeronimo; University of Burgos, Health Sciences Collazo-Riobo, Carla ; University of Burgos, Health Sciences Jahouh, Maha; Universidad de Burgos, Health Sciences Bravo-Anguiano, Yolanda; Universitary Hospital of Burgos, Neurology Trejo-Gabriel-Galan, Jose M; Universitary Hospital of Burgos, Neurology
Keywords:	NEUROLOGY, Stroke < NEUROLOGY, REHABILITATION MEDICINE

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1  
2  
3 **TITLE:** Effects of Mirror Therapy and Cognitive Therapeutic Exercise on the  
4 improvement of the upper extremity functions in stroke patients: a randomized clinical  
5 trial protocol  
6  
7  
8  
9

10 **AUTHORS:**

- 11 • Josefa Gonzalez-Santos, PhD.<sup>1</sup>
- 12 • Raul Soto-Camara, MSN, PhD.<sup>1-2</sup>
- 13 • Paula Rodriguez-Fernandez, OT.<sup>1</sup>
- 14 • Maria Jimenez-Barríos, OT.<sup>1</sup>
- 15 • Jeronimo Gonzalez-Bernal, PhD.<sup>1</sup>
- 16 • Carla Collazo-Riobo, OT.<sup>1</sup>
- 17 • Maha Jahouh, OT.<sup>1</sup>
- 18 • Yolanda Bravo-Anguiano, MD, Neurologist.<sup>3</sup>
- 19 • Jose M Trejo-Gabriel-Galán, MD, Neurologist, Phd.<sup>3</sup>
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29

30 **AUTHOR AFFILIATIONS:**

- 31 1. Department of Health Sciences, University of Burgos, Spain.
- 32 2. Emergency Medical Service, Health Service of Castilla y León, Burgos, Spain.
- 33 3. Neurology Department, University Hospital of Burgos, Spain.
- 34
- 35
- 36
- 37
- 38

39 **CORRESPONDENCE AUTHORS:**

- 40 • Raúl Soto-Cámara
- 41 Department of Health Sciences, University of Burgos, Spain.
- 42 Paseo de los Comentadores s/n
- 43 09001 - Burgos (Spain)
- 44 E-mail: [rscamara@ubu.es](mailto:rscamara@ubu.es)
- 45 Phone number: +34 669 256957
- 46
- 47
- 48
- 49
- 50
- 51
- 52

53 **WORD COUNT:** 3.640  
54  
55  
56  
57  
58  
59  
60

## ABSTRACT

**Introduction:** Stroke has one of the highest incidence rates out of all pathologies. It affects the patient's quality of life and liberty, thus provoking a variety of alterations and severities of disability and dependence. The brain, conceptualized in terms of neuroplasticity, is capable of reorganizing new neuronal pathways. On that basis, recent neuro-rehabilitation techniques like Mirror Therapy (MT), Cognitive Therapeutic Exercise (CTE) and Task-Oriented Motor Learning (TOML) have been designed to improve the motor functions of the affected upper limb in post-stroke patients with residual hemiparesis, being the objective of this study evaluate and compare their effectiveness.

**Methods and analysis:** This study has been designed as a randomized clinical trial with 3 parallel groups, including 154 stroke patients over 18 years of age. The principal variable will be the functionality of the affected upper limb, while the secondary variables will include cognitive performance, emotional state, quality of life, and daily life activities (DLA). The intervention groups will receive a treatment, based either on MT or CTE, both combined with TOML. No additional interventions will be applied to the control group. All the variables will be evaluated in the initial visit and follow-up visits held in the 6<sup>th</sup> and 13<sup>th</sup> week. The recruitment of participants will commence on first January 2020 and the study will be conducted for 18 months.

**Ethics and dissemination:** This protocol has been approved by the Research Ethics Committee of the Health Area of Burgos and Soria (Spain) in June 2019 (CEIm 2.134/2.019). The SPIRIT checklist protocol will be applicable to the study. This clinical trial has been registered with ClinicalTrials.gov of the National Library of Medicine of the United States, with the identifier NCT04163666. The results will be disseminated through open-access peer-reviewed scientific journals, presentations at conferences and seminars, and through communications like media and social networks.

**Keywords:** stroke, upper limb, neuro-rehabilitation, mirror therapy, therapeutic cognitive exercise, task-oriented motor learning, Perfetti method.

## STRENGTHS AND LIMITATIONS OF THE STUDY

- This study will use stroke-related neuro-rehabilitation techniques, which would enable an easy at-home application by the patient.
- The functionality of the affected upper extremities, cognitive performance, emotional state, quality of life, and the performance of everyday activities will be assessed using validated instruments.
- This is not a blind study for the participants, owing to the nature of the intervention, although it will be applicable for the researchers performing the evaluations and the statistical analysis.

## INTRODUCTION

The World Health Organization (WHO) defines stroke as a clinical syndrome of vascular origin, characterized by the rapid development of signs of focal and, on occasions, overall neurologic deficit, lasting for over 24 h<sup>1</sup>.

It forms one of the most frequent reasons requiring urgent neurological assistance and the principal cause of physical disability, after dementia, among adults<sup>2</sup>. Sixty-eight percent of the stroke-affected patients have difficulties in performing Basic Daily Living Activities (BDLA)<sup>3</sup>, as a result of sensory-based motor disorders, perception disorders, language and communication problems, and emotional, psychological, and behavioral disorders<sup>4-6</sup>.

Weakness (hemiparesis) or paralysis (hemiplegia) of a side of the body contrary to the injured side is the first sequela of stroke in 80% of the patients<sup>4-5,7</sup>. Hemiparesis of the upper extremities, the most frequent cause of functional disability, includes altered sensitivity, weakness, varied motor control, and spasticity. It limits the performance of Daily Living Activities (DLA), which has a significant impact on the quality of life of stroke patients<sup>8</sup>.

In the stroke rehabilitation process, special emphasis must be given to the functional and motor recovery of the affected upper extremity, essential for the performance of DLA<sup>9</sup>. It usually commences with spontaneous recovery during the first month, followed by learning-assisted recovery over the next six months, although, it has been demonstrated that results can be achieved even in the most chronic phases because of cerebral plasticity and motor-related sensory learning<sup>3,9-12</sup>. Most studies have demonstrated the importance of patient-centered interventions, as well as the need to

1  
2  
3 combine different techniques, thereby not centering the treatment on a single  
4 modality<sup>10,13-14</sup>.

5  
6  
7 The present study has been designed to use both Mirror Therapy (MT) and Cognitive  
8 Therapeutic Exercise (CTE), in combination with Task-Oriented Motor Learning  
9 (TOML).

10  
11  
12 MT, developed by Ramachandran and Rogers-Ramachandran<sup>15</sup>, owes the objective of  
13 improving motor functions of the affected upper extremities, by guiding the patient such  
14 that attention is centered on the reflection of the healthy upper limb in a mirror as if it  
15 were the affected member<sup>6</sup>. Observation of normal movements in the mirror provides  
16 positive visual feedback, while also increasing the flow of proprioceptive information  
17 and activating the neurons and the pre-motor cortex, thus improving the functionality of  
18 the affected upper extremity<sup>16-18</sup>.

19  
20  
21 Over the recent years, numerous studies have demonstrated the benefits of MT in the  
22 rehabilitation of upper-limb motor functions, the performance of DLA, and stroke-  
23 patient pain thresholds<sup>16-23</sup>. Oliveira and Castro et al.<sup>24</sup> were unable to prove its  
24 effectiveness, despite improvements in self-care, because those improvements were not  
25 statistically significant.

26  
27  
28 Factors such as age, cognitive capability, and finger-related motor functioning of the  
29 affected or dominant hand can influence the degree of effectiveness of MT in patients  
30 with hemiparesis<sup>7</sup>. Therefore, the majority of studies coincide over the need for further  
31 research in this area<sup>16-24</sup>.

32  
33  
34 CTE or the Perfetti method is a cognitive rehabilitation modality, the objective of which  
35 is to achieve motor recovery, by using afferent information of a proprioceptive and/or  
36 tactile type. The patient is expected to center the mind on parts or specific  
37 characteristics of the body while attempting to solve a cognitive problem that is  
38 described by the therapist. It is presented to the patient as the preparation of a perceptive  
39 hypothesis, in such a way that the patient consciously perceives the upper limb in a  
40 manner that favors the re-learning of a motor action that has been lost by the nervous  
41 system<sup>25</sup>.

42  
43  
44 CTE has demonstrated its effectiveness in improving muscle strength, tactile sensorial  
45 discrimination and kinesthetics, the functionality of the upper hemiplegic or hemiparetic  
46 extremities, and the quality of life of stroke patients<sup>26-29</sup>. However, despite the fact that  
47 it is one of the most complete and effective methods for the rehabilitation of  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 neurological deficit in the upper extremities<sup>26</sup>, new studies with homogeneous samples  
4 of greater size are warranted, which could define aspects such as the time and the  
5 materials necessary for their implementation<sup>25-27</sup>.  
6  
7

8 TOML is an effective method to promote and stimulate motor skills and neuronal  
9 plasticity in patients with injuries to the Central Nervous System (CNS). It comprises  
10 screening of the patient to develop personal strategies for performing useful functional  
11 movements in different contexts and situations<sup>29</sup>. Training of the paretic hemibody is  
12 performed under suitable conditions through specific, repetitive, and intensive tasks, of  
13 significance to the patient<sup>29-32</sup>. By actively participating in the rehabilitation process,  
14 intervening in the search and the discovery of strategies, personal functional  
15 independence is improved and the adaptation of the patient to the environment is  
16 assisted<sup>29</sup>. This rehabilitation technique employs five strategies to teach and motivate  
17 the patient, who must adapt to the requirements of each task: verbal instructions, visual  
18 demonstrations, manual guide, reinforcement, and positive feedback, and its repetitive  
19 practice in different contexts<sup>13</sup>.  
20  
21  
22  
23  
24  
25  
26  
27  
28

29 Despite the sparse scientific evidence of this field in literature, it has been demonstrated  
30 that therapies with task-oriented functions facilitate greater functional recovery of the  
31 upper extremities. Therefore, a therapeutic approach based on TOML that stimulates the  
32 potential neuroplasticity of SNCE, combined with techniques such as MT and CTE, will  
33 be of greater use in improving the motor function than the treatments based on a  
34 specific approach or a concrete technique<sup>29,31,33-36</sup>.  
35  
36  
37  
38  
39

40 In view of the above, a comparative study between MT and CTE has been planned.  
41 Even though these two techniques are effective in neuro-rehabilitation, their  
42 comparative effectiveness, or the answer to the question as to which one would yield  
43 better results, as well as their maintenance over time is yet to be confirmed. The  
44 objective of the present study is, therefore, to analyze and compare the effectiveness of  
45 MT and CTE, in combination with TOML, in the optimization of the upper extremities  
46 of stroke patients with residual hemiparesis and their movement patterns, in such a  
47 manner so as to achieve maximum functionality of the upper extremity, correct the  
48 improper compensation strategies and achieve functionally useful movements.  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## METHODS AND ANALYSIS

### Design and setting

This is a controlled, randomized clinical test that would comprise three parallel groups (control, intervention 1 and intervention 2). Participant enrollment will begin on first January 2020 and will last for 18 months. An initial evaluation will be completed and two follow-up visits at week 6 and 13 would be carried out.

### Study population

The enrollment of participants will commence at the Neurological Service and Stroke Unit of the University Hospital of Burgos (HUBU), by means of consecutive sampling. HUBU is the only third-level health center for the referral of stroke patients in the region. All other actions would be carried out at the patient's home.

All participants meeting the following inclusion criteria would be included in the study: patients of both sexes, aged 18 years or above, with a diagnosis of residual hemiparesis due to ischemic or hemorrhagic stroke, whose movements of the affected upper extremities are classified between stages II and IV on the Brunnstrom Scale<sup>37</sup>, with a score on the Montreal Cognitive Assessment (MoCA) scale<sup>38</sup> equal to or over 26. All participants will require to sign an informed consent form. Participants presenting heminegligence, Wernicke's aphasia, and visual deficits (homonymous hemianopsia) will be excluded from the study.

### Patient and public involvement

The patients and the public will neither participate in the study design, nor in the data-collection process. The results will be disseminated through communications including media, health-care institutions, patients' associations with which collaborative agreements are in place, and during meetings organized for sharing information with the participants of the study.

### Estimation of the sample size

The sample size of the Control Group (CG) and the Intervention Group (IG) will be estimated, using the following factors: an  $\alpha$  risk of 5% and a statistical power of 80%, both in bilateral tests, with an expected loss percentage of 10% in the follow-up phase. The inferiority study is expected to have a margin of 25%, with expected responses of 50% for the principal variable (functionality of upper member) in the MT group and the same proportion in the CTE group, where both therapies will be combined with TOML.

1  
2  
3 It has been estimated that 55 participants would be required in each intervention group.  
4 An additional 44 individuals will be needed for the calculation of the size of the  
5 spontaneous improvement group, which is bound to occur in 20% of the cases as per the  
6 estimates<sup>39</sup>.  
7  
8  
9

### 10 **Randomization**

11  
12 Participants will randomly be assigned either to a CG or IG. An assignation sequence  
13 with masking clusters, in a ratio of 1/1/1, will be centrally generated by an independent  
14 researcher using the Eidata 4.2 program, before the inclusion of the participants.  
15  
16

### 17 **Intervention**

18  
19 The standard rehabilitation treatment would be applied to this condition. No additional  
20 intervention for the CG participants will be included.  
21  
22

23 IG-1 will receive an additional treatment based on MT+TOML, whereas IG-2 group  
24 will be based on CTE+TOML therapies. In either of the groups, the progression of  
25 interventions will begin at the participant's house over a period of six weeks (30 days),  
26 involving 60-min sessions, 30 of which will be for MT and CTE, while the remaining  
27 30 min will be for TOML.  
28  
29

30  
31 Tasks for the TOML will be presented sequentially in a structured manner along with  
32 their specific characteristics, which would change from one session to another to  
33 facilitate their application in daily life. The complex activities will be segmented into  
34 simpler tasks to facilitate their learning. Verbal instructions and/or presentations will be  
35 provided, thereby gradually decreasing the support. Every day of the week will be  
36 dedicated to a BDLA, with short rest periods, progressively increasing its difficulty. The  
37 last week will be meant for tasks and BDLA that the patient might request and which  
38 can be performed at home.  
39  
40  
41  
42  
43  
44  
45

46 The patient will be seated on an ordinary chair in the MT, with their forearms resting on  
47 a table. A mirror will be placed between both the arms, at a right angle to the torso. The  
48 affected member must be placed behind the mirror, in a comfortable position, in such a  
49 way that the patient cannot see it. The healthy member must be placed in a position as  
50 similar as possible to the affected member so that it is completely reflected in the mirror  
51 with no distortion of the image. Any object or symbol that identifies the healthy  
52 member must be removed or covered up. Simple movements will be performed without  
53 any objects during the first 10 sessions, progressively introducing simple movements  
54 and objects in the following 10 sessions; this will progressively include movements of  
55  
56  
57  
58  
59  
60

1  
2  
3 greater complexity with objects over the last 10 sessions. To be more specific, the  
4 patient will complete movements with a healthy hand throughout the first 3 sessions in  
5 groups of 10 and will try to imagine them with the affected hand. Those movements  
6 will be assisted by a therapist in the three subsequent sessions, while the patient,  
7 focusing on the affected hand, will try to imitate the movements of the healthy hand  
8 throughout the last 4 sessions. All the exercises will have to be completed slowly and  
9 repeated at least 15 times. The activities and their levels of complexity will be adapted  
10 to the limitations and capabilities of each patient.  
11

12  
13  
14  
15  
16  
17 Three different modalities will be used in accordance with the function of the  
18 pathological element to be recovered. With the first modality (first degree), an attempt  
19 will be made to control the exaggerated resistance of muscle tonicity to passive  
20 stretching and to surmount the deficits of tactile and kinesthetic sensitivity rather than  
21 the patient activating a particular motor unit, the therapist will manipulate the whole  
22 movement. Throughout the second modality (second degree), an attempt will be made  
23 to control the involuntary activation of muscle groups, not directly involved with the  
24 action that has been performed, including inferences of weight, grip, and friction, with  
25 minimum assistance from the therapist. It will be introduced in combination with the  
26 movements from the first-degree modality, when the patient will have acquired a certain  
27 degree of control over the recruitment of motor units. In the third-degree modality, the  
28 control of voluntary movements and decisions on their fragmentation, variability, and  
29 adaptation, with the objective of perfect automatization of the movement, all without the  
30 therapist will be emphasized; it is anticipated that all the exaggerated responses should  
31 have been achieved in the earlier exercises. The sessions will commence with exercises  
32 from the first-degree modality, progressively increasing the degree of difficulty, in  
33 accordance with the improvements observed and the needs of the patient. All the  
34 exercises used in one modality can be adapted to another.  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

#### 48 **Procedure**

49  
50 An initial evaluation visit will be programmed for the 4th week after stroke and two  
51 follow-up visits in the 6<sup>th</sup> and 13<sup>th</sup> weeks after the initial visit, in which an assessment of  
52 their state will be completed with the help of different instruments and questionnaires.  
53 All participants included in the IG will receive 30 treatment sessions, distributed  
54 between the initial evaluation and the first follow-up visit (Figure 1).  
55  
56  
57  
58  
59  
60

### Primary and secondary endpoints

The principal variable would be the improvement in the functionality of the affected upper extremity; the secondary variables will include cognitive performance, emotional state, quality of life, and performance of DLA. All these variables will be assessed during the initial evaluation visit, through the use of questionnaires, previously validated for the Spanish population, during the follow-up visits.

#### *The functionality of the affected upper extremity*

The different motor deficit components of the affected upper limb will be assessed by utilizing five scales:

- The Fugl-Meyer Scale<sup>40</sup>, which assesses motor functioning, passive articular mobility, articular pain, coordination, and balance.
- The Action Research Arm Test (ARAT)<sup>41</sup>, which measures the functionality of the upper limb.
- The Motor Activity Log (MAL-30)<sup>41</sup>, which assesses the quantity (subscale CU) and the quality (CM scale) of use of hand and arms during the performance of DLA.
- The Block and Box Test (BBT)<sup>42</sup>, which assesses the manipulative value of the hand.
- The Ashworth Scale<sup>43</sup>, which measures the spasticity of the upper limb.

#### *Cognitive performance*

The cognitive performance will be evaluated by the MoCA scale<sup>38</sup>, distributed into seven different cognitive domains: visuo-spatial executive capacity, denomination, language attention, abstraction, learning, and deferred learning, recall, and orientation.

#### *Emotional state and quality of life*

Emotional state and quality of life will be evaluated using the Escala de Calidad de Vida para el Ictus (ECVI-38) [Scale of Post-Stroke Quality of Life]<sup>44</sup>, which comprises 38 items grouped into 8 domains: physical state, communication, cognition, emotions, feelings, BDLA, common DLA, and socio-family functioning.

#### *Performance of DLA.*

BDLA will be evaluated via the Functional Independence Measure (FIM) and its extension, the Functional Assessment Measure (FAM), designed specifically for patients with cerebral damage<sup>45</sup>. The 30 items in this instrument are used to assess the

1  
2  
3 self-care tasks inherent to DLA, motor, cognitive, and behavioral functions, and  
4 communicative and functional behavior in the community.  
5

6  
7 The instrumental activities of daily living (IADL) will be evaluated using the Lawton-  
8 Brody index<sup>46</sup>. It assesses the capability to develop tasks involving the handling of  
9 every-day utensils and day-to-day social activities, including the use of telephone,  
10 shopping, preparing meals, household work, washing clothes, use of transport,  
11 responsibility with respect to medication, and the management of economic affairs.  
12  
13

#### 14 *Other measures/co-variables*

15  
16 The following variables will be evaluated to control for possible predictive or confusion  
17 factors: age, sex, type of stroke, affected cerebral hemisphere and stroke severity as  
18 quantified by the National Institute Health Stroke Scale (NIHSS)<sup>47</sup>.  
19  
20  
21

#### 22 **Data-collection, data-management, and follow-up procedure**

23  
24 The initial evaluation visit, the follow-up visits, and the intervention visits will be  
25 completed by properly trained therapists who would follow the standardized  
26 methodological criteria mentioned in the data collection manual. Different therapists  
27 would be engaged in providing treatment and conducting the initial visits. Each  
28 participant will be assigned a unique intervention code for the purposes of the study. All  
29 the assessments would be entered into a safe and secure data-collection notebook. A  
30 database would be created using SPSS software, accessible only to the research team  
31 members and the ones involved in the statistical analysis of the study. A researcher will,  
32 on a weekly basis, monitor the inclusion of new patients, debugging, testing, checking  
33 the databases, and adaption of protocol procedures. Double-entry of data will be carried  
34 out to maintain a low error rate.  
35  
36  
37  
38  
39  
40  
41  
42  
43

#### 44 **Blinding strategy**

45  
46 This is not a blind study, owing to the nature of the intervention, the participants, and  
47 the fact that the researcher is responsible for conducting the therapy. However,  
48 strategies will be implemented to ensure that it is as blind a study as possible. Different  
49 researchers will be employed for carrying out the assessment visits and conduction of  
50 the therapy, regardless of the group to which the participants belong. In addition, clear  
51 instructions will be given to the participants, not to reveal the group to which they have  
52 been assigned during the assessment visits. The researcher responsible for statistical  
53 analysis will be blinded to the participant's group.  
54  
55  
56  
57  
58  
59  
60

## Statistical analysis

The analysis of the results will be done by intention-to-treat (ITT) to control for the effects of non-random abandonment. The average and standard deviation values will be used for the description of the quantitative variables, and distribution of frequencies and percentages for the qualitative variables. The association between independent qualitative variables will be analyzed by means of Yate's chi-squared test with correction for continuity and, if the calculated effects are less than 5, Fisher's exact test would be used.

The assumptions necessary for applying parametric tests (Normality, Homoscedasticity, and the Runs Test) will be confirmed. Multivariate analyses (MANCOVAs) will be conducted to test the global effect of the interventions, and univariate analyses of covariance (ANCOVAs) will be employed to test the particular effects of experimental conditions in each of the dependent variables of investigation. The average scores of indicators from each analysis, obtained in both, the pre-test and the post-test 1 will be included. The heterogeneity caused in the dependent variables as a result of the influence of the aforementioned co-variables will thereby be eliminated.

All the analyses will be done using SPSS V.25.0 software (IBM), establishing an  $\alpha$  risk of 0.05 as the limit of statistical significance.

## ETHICS AND DISSEMINATION

### Ethical considerations

The study has been approved by the Ethics Committee for Research involving Medication of the Health Area of Burgos and Soria (Spain), in June 2019 (CEIm 2.134/2.019). A SPIRIT Declaration checklist is available for this protocol. The clinical test has been registered at ClinicalTrials.gov with the identifier NCT04163666.

In accordance with the Helsinki Declaration, prior informed consent will be sought from the individuals who voluntarily decide to participate. They will be informed of the objectives, the risks, and benefits of the assessments, as well as the interventions that will be involved. None of the actions imply additional risks to the life of the participants. At all times, the confidentiality of the data will be guaranteed in accordance with the current legislation.

### Dissemination plan

The dissemination of results will follow the recommendations mentioned in the CONSORT declaration. The researchers will have their study published in open access peer-reviewed scientific journals, so as to acquire the highest possible visibility for the study. At least two publications are expected to be completed, one of the results of the principal variable (functionality of the upper limb) and the other on the secondary results. The result dissemination will be done through communications including media and social networks, as well as at international and national scientific conferences and seminars. Likewise, a doctoral thesis based on the content of this project will be developed.

### DISCUSSION

At present, a number of rehabilitative methods prevail, based on the principle of cerebral plasticity. Among these, MT and CTE promote the recovery of the affected upper limb.

Various clinical tests have demonstrated that MT is an effective treatment for the recovery of the upper limb in sub-acute stroke patients<sup>16-23</sup>. The review completed by Lisalde-Rodríguez<sup>48</sup> demonstrated that MT combined with conventional therapy was effective in improving the motor function of the upper paretic limb, but not the overall functionality of the patient. In another study, MT and TOML were combined within the same treatment session, and statistically significant results were observed in the functionality of the upper extremity and the performance of DLA in the patient<sup>31</sup>. The study by Kyunghoon et al.<sup>9</sup> involving 25 stroke patients confirmed the effectiveness of an intervention based on MT combined with TOML, in comparison to the conventional therapy. The former treatment proved to be the most effective in rehabilitation of the affected upper limb functionality and performance of DLA.

CTE, despite having demonstrated its effectiveness in the execution of simple motor activities like cylindrical grip, lacks evidence on its repercussions on the recovery of distal functions of greater complexity among patients with affected upper extremities following a stroke ictus<sup>26</sup>.

The present literature, though relates both the treatment techniques, presents significant limitations such as the lack of specificity on the level of deficit affecting the upper limb, sample size, and the control groups. It is necessary to ascertain the correct execution and

1  
2  
3 description of activities, processes, and exercises for their development and, likewise, to  
4 validate future investigations on a scientific basis. No studies so far have demonstrated  
5 which out of the two techniques is the most effective in achieving functional recovery of  
6 the affected upper extremity.  
7  
8  
9

10 This work will provide novel and useful data for the development of post-stroke  
11 rehabilitation strategies. The intervention may provide implications for the preparation  
12 of evidence-based recommendations, practical clinical guides, and continuous quality  
13 improvement programs that target post-stroke patients.  
14  
15  
16  
17  
18  
19  
20

21 **Authors' contributions:** JGS, PRF, MJB, CCR and MJ devised the design of the study.  
22 JGB, PRF, MJB and RSC prepared and developed the protocol study. JGS, JGB and  
23 RSC provided methodological assistance and statistical assessment. YBA and JMTGG  
24 provided a critical review of the paper. All the authors have read and accepted the final  
25 version of the protocol.  
26  
27  
28  
29

30  
31 **Funding:** This research will receive no specific grant from any funding agency in the  
32 public, commercial or not-for-profit sectors.  
33  
34  
35  
36

37 **Competing interests:** None declared.  
38  
39  
40  
41  
42

#### 43 **Legends of figures:**

- 44 • **Figure 1:** Study flow chart.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## REFERENCES

1. Hetano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ.* 1976;54(5):541–53.
2. Organización Mundial de la Salud (OMS) [sede Web]. Who; 2017. Enfermedades cardiovasculares.  
Available at: [https://www.who.int/es/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/es/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds))
3. Fernández Gómez E, Ruiz Sancho A, Sánchez Cabeza A. Terapia ocupacional en daño cerebral adquirido. *TOG.* 2009;6(4):410–64.
4. Polonio López B, Romero Ayuso DM. Terapia Ocupacional aplicada al daño cerebral adquirido. Madrid: Editorial Médica Panamericana, SA; 2010.
5. Clavel González A. Rehabilitación de miembro superior tras un ictus a través de entrenamiento de actividades de la vida diaria. *TOG.* 2016;13(24):1–17.
6. Ministerio de Sanidad y Política Social. Guía de Práctica Clínica para el manejo de pacientes con ictus en Atención Primaria. Madrid; 2009.
7. Brunetti M, Morkisch N, Fritzsche C et al. Potential determinants of efficacy of mirror therapy in stroke patients. A pilot study. *Restor Neurol Neurosci.* 2015;33(4):421–34. doi: 10.3233 / RNN-140421.
8. Fernández Gómez E, Sánchez Cabeza A. Motor imagery: a systematic review of its effectiveness in the rehabilitation of the upper limb following a stroke. *Rev Neurol.* 2018;66(5):137–46.
9. Kyunghoon K, Sukmin L, Donghoon K et al. Effects of mirror therapy combined with motor tasks on upper extremity function and activities daily living of stroke patients. *J Phys Ther Sci.* 2016;28(2):483–87. doi: 10.1589 / jpts.28.483
10. Domínguez Ros Y, Elmacouti Bouhsain M, Villareal Salcedo I et al. Plan de intervención desde Terapia Ocupacional en un paciente afecto de hemiplejía derecha: tratamiento rehabilitador centrado en la funcionalidad de la extremidad superior. *TOG.* 2017;14(26):520–8.
11. Murie Fernández M, Irimia P, Martínez Vila E et al. Neuro-rehabilitation after stroke. *Rev Neurol.* 2010;25(3):189–96.
12. Cardenal Félix G, Roca Bauzá I. Tratamiento del ictus con Terapia Ocupacional y Fisioterapia. *Rev Astur Ter Ocu.* 2009;(7):9–13.

13. Flórez García, MT. I Interventions to improve motor function in stroke patients.. *Rehabilitación*. 2000;34(6):423–37.
14. Hernández Molina L. Terapia Ocupacional para la independencia en las actividades de la vida diaria en accidente cerebrovascular. *TOG*. 2013;10(7):1–31.
15. Radajewska A, Opara JA, Kucio C et al. 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.
16. Paik YR, Kim SK, Lee JS et al. Simple and task-oriented Mirror Therapy for upper extremity function in stroke patients: A pilot study. *Hong Kong J Occup Th*. 2014;24(1):6–12.
17. Toh SFM, Fong KNK. Systematic review on the effectiveness of mirror therapy in training upper limb hemiparesis after stroke. *Hong Kong J Occup Th*. 2012;22(1): 84–95.
18. Novaes MM, Palhano-Fontes F, Peres A et al. Neurofunctional changes after a single mirror therapy intervention in chronic ischemic stroke. *Int J Neurosci*. 2018;128(10):966–74. doi: 10.1080 / 00207454.2018.1447571.
19. Fukumura K, Sugawara K, Tanabe S et al. Influence of mirror therapy on human motor cortex. *Int J Neurosci*. 2007;117(7):1039–48.
20. Bai Z, Zhang J, Zhang Z et al. 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):1–10. doi: 10.3389 / fneur.2019.00288.
21. Zeng W, Guo Y, Wu G et al. Mirror therapy for motor function of the upper extremity in patients with stroke: A meta-analysis. *J Rehabil Med*. 2018;50(1):8–15. doi: 10.2340 / 16501977-2287.
22. Da Silva Costa V, Cunha da Silveira JC, Albuquerque Clementino TC et al. Effects of mirror therapy on the motor and functional recovery of post-stroke paretic upper limbs: A systematic review. *Fisioter Pesqui*. 2016;23(4):431–8.
23. Jin-Young P, Moonyoung C, Kyeong-Mi K et al. The effect of mirror therapy on upper-extremity function and activities of daily living in stroke patients. *J Phys Ther Sci*. 2015;27(6):1681–83. doi: 10.1589 / jpts.27.1681.
24. Oliveira e Castro P, Ferreira Pereira da Silva Martins MM et al. Mirror therapy and self-care autonomy after stroke: an intervention program. *Revista de Enfermagem Referência*. 2018;4(17):95–106.

- 1  
2  
3 25. Domínguez Ferraz D, Da Silva-Ribeiro NM, De Matos-Pinheiro I et al. Eficacia del  
4 método Perfetti en el tratamiento de secuelas del accidente cerebrovascular: una  
5 revisión sistemática. *Cuest. fisioter.* 2014;43(3):196–205.
- 6  
7  
8 26. Díaz Castro WM, Rodríguez López YC. Método Perfetti como estrategia terapéutica  
9 en la rehabilitación de pacientes con enfermedad cerebrovascular: Revisión  
10 bibliográfica. *Movimiento Científico.* 2019;13(1):65–70.
- 11  
12  
13 27. Laia Sallés L, Martín-Casas P, Gironès X et al. A neurocognitive approach for  
14 recovering upper extremity movement following subacute stroke: A randomized  
15 controlled pilot study. *J Phys Ther Sci.* 2017;29(4):665–72. doi: 10.1589 /  
16 jpts.29.665.
- 17  
18  
19 28. Lee S, Bae S, Jeon D et al. The effects of cognitive exercise therapy on chronic  
20 stroke patients' upper limb functions, activities of daily living and quality of life. *J*  
21 *Phys Ther Sci.* 2015;27(9):2787–91. doi: 10.1589 / jpts.27.2787.
- 22  
23  
24 29. Cano de la Cuerda R, Molero Sánchez A, Carratalá Tejada M et al. Theories and  
25 control models and motor learning: clinical applications in neuro-rehabilitation. *Rev*  
26 *Neurol.* 2015;30(1):32–41. doi: 10.1016 / j.nrl.2011.12.010.
- 27  
28  
29 30. Preissner K. Use of the occupational therapy task-oriented approach to optimize the  
30 motor performance of a client with cognitive limitations. *Am J Occup Ther.*  
31 2010;64(5):727–34. doi: 10.5014/ajot.2010.08026
- 32  
33  
34 31. Khandare SS, Singaravelan RM, Khatri SM. Comparison of task specific exercises  
35 and mirror therapy to improve upper limb function in subacute stroke patients. *J*  
36 *Med Dent Sci.* 2013;7(1):5–14.
- 37  
38  
39 32. Mathiowetz VG, White M, del Mas RC. Efficacy of occupational therapy task-  
40 oriented approach in upper extremity post-stroke rehabilitation. *Occup Ther Int.*  
41 2016;23(4):444–56. doi: 10.1002 / oti.1447.
- 42  
43  
44 33. Bayón Calatayud M, Gil Agudo A, Benavente Valdepeñas AM et al. Efficacy of  
45 new therapies for upper limb neurorehabilitation in stroke patients. *Rehabilitación.*  
46 2014;48(4):232–40.
- 47  
48  
49 34. Arias Cuadrado A. Rehabilitación del ACV: evaluación, pronóstico y tratamiento.  
50 *Galicia Clin.* 2009;70(3):25–40.
- 51  
52  
53 35. Fernández Gómez E, Ruiz Sancho A, Sánchez Márquez G. Tratamiento de la  
54 extremidad superior en la hemiplejía desde terapia ocupacional. *TOG.*  
55 2010;7(11):1–24.
- 56  
57  
58  
59  
60

- 1  
2  
3 36. Michaelsen SM, Dannenbaum R, Levin MF. Task-specific training with trunk  
4 restraint on arm recovery in stroke: Randomized control trial. *Stroke*.  
5 2006;37(1):186–92.  
6  
7
- 8 37. Vandana, Pattnaik M, Mohanty P. Effectiveness of mirror therapy in rehabilitation  
9 of hand function in sub-acute stroke. *Palliat Med Care*. 2017;4(2):1–8.  
10
- 11 38. Ojeda del Pozo N, del Pino Sáez R, Ibarretxe Bilbao N et al. Test Montreal  
12 Cognitive Assessment Test: normalization and standardization for Spanish  
13 population. *Rev Neurol*. 2016;63(11):488–96.  
14  
15
- 16 39. Kwakkel G, Kollen B, Twisk J. Impact of time on improvement of outcome after  
17 stroke. *Stroke*. 2006;37(9):2348–53.  
18  
19
- 20 40. Ferrer González BM. Adaptación y validación al español de la escala Fugl-Meyer en  
21 el manejo de la rehabilitación de pacientes con ictus [Doctoral thesis]. Universidad  
22 de Sevilla: 2016.  
23  
24
- 25 41. Doussoulin-Sanhueza A, Rivas-Sanhueza R. Validation and use Motor Activity Log  
26 and Action Research Arm scales as tools to assess V at d u Mo cti y o n Res ch A m  
27 s ess i n an L o ear a l the function of the paretic upper limb after a stroke in clinic  
28 and research. *Rev Mex Neurocienc*. 2014;15(2):138–46.  
29  
30
- 31 42. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and  
32 Block Test of manual dexterity. *Am J Occup Ther*. 1985;39(6):386–91. doi:  
33 10.5014/ajot.39.6.386  
34  
35
- 36 43. Gómez-Soriano J, Cano-de-la-Cuerda R, Muñoz-Hellín E et al. Evaluation and  
37 quantification of spasticity: a review of the clinical, biomechanical and  
38 neurophysiological methods. *Rev Neurol*. 2012;55(4):217–26.  
39  
40
- 41 44. Fernández-Concepción O, Román-Pastoriza Y, Álvarez González MA et al. The  
42 development of a scale to evaluate the quality of life in stroke survivors. *Rev*  
43 *Neurol*. 2004;39(10):915–23  
44  
45
- 46 45. Domínguez Morales MR, Balmaseda Serrano R, León Carrión J et al. Functional  
47 recovery of cerebrovascular patients after intensive treatment: preliminary data.  
48 *Revista Española de Neuropsicología*. 2012;2(3):44–61.  
49  
50
- 51 46. Jiménez-Caballero P, López-Espuela F, Portilla-Cuenca J et al. Evaluation of the  
52 instrumental activities of daily living following a stroke by means of the Lawton and  
53 Brody scale. *Rev Neurol*. 2012;55(6):337–42.  
54  
55
- 56 47. Montaner J, Alvarez-Sabin J. NIH stroke scale and its adaptation to Spanish.  
57 *Neurologia*. 2006;21(4):192–202.  
58  
59  
60

1  
2  
3 48. Lisalde Rodríguez ME, García Fernández JA. Mirror therapy in hemiplegic patient.  
4  
5 *Rev Neurol.* 2016;62(1):28–36.  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial- protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym - <i>Pag 1</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry - <i>Pag 11</i>
	2b	All items from the World Health Organization Trial Registration Data Set - - <i>Pag 11</i>
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support - <i>Pag 13</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors - <i>Pag 1</i>
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
<b>Introduction</b>		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention - <i>Pag 3-5</i>
	6b	Explanation for choice of comparators - <i>Pag 3-5</i>
Objectives	7	Specific objectives or hypotheses - <i>Pag 5</i>

1  
2 Trial design 8 Description of trial design including type of trial (eg, parallel group,  
3 crossover, factorial, single group), allocation ratio, and framework (eg,  
4 superiority, equivalence, noninferiority, exploratory) - *Pag 6*  
5  
6  
7

8 **Methods: Participants, interventions, and outcomes**  
9

10 Study setting 9 Description of study settings (eg, community clinic, academic hospital)  
11 and list of countries where data will be collected. Reference to where  
12 list of study sites can be obtained - *Pag 6*  
13

14 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility  
15 criteria for study centres and individuals who will perform the  
16 interventions (eg, surgeons, psychotherapists) - *Pag 6*  
17  
18

19 Interventions 11a Interventions for each group with sufficient detail to allow replication,  
20 including how and when they will be administered - *Pag 7-8*  
21

22 11b Criteria for discontinuing or modifying allocated interventions for a  
23 given trial participant (eg, drug dose change in response to harms,  
24 participant request, or improving/worsening disease)  
25

26 11c Strategies to improve adherence to intervention protocols, and any  
27 procedures for monitoring adherence (eg, drug tablet return,  
28 laboratory tests)  
29

30 11d Relevant concomitant care and interventions that are permitted or  
31 prohibited during the trial  
32  
33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific  
35 measurement variable (eg, systolic blood pressure), analysis metric  
36 (eg, change from baseline, final value, time to event), method of  
37 aggregation (eg, median, proportion), and time point for each  
38 outcome. Explanation of the clinical relevance of chosen efficacy and  
39 harm outcomes is strongly recommended - *Pag 9-10*  
40  
41

42 Participant 13 Time schedule of enrolment, interventions (including any run-ins and  
43 timeline washouts), assessments, and visits for participants. A schematic  
44 diagram is highly recommended (see Figure) - *Pag 8 - Pag 10*  
45

46 Sample size 14 Estimated number of participants needed to achieve study objectives  
47 and how it was determined, including clinical and statistical  
48 assumptions supporting any sample size calculations - *Pag 6*  
49  
50

51 Recruitment 15 Strategies for achieving adequate participant enrolment to reach  
52 target sample size - *Pag 6*  
53

54 **Methods: Assignment of interventions (for controlled trials)**  
55

56 Allocation:  
57  
58  
59  
60

1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions - <i>Pag 7</i>
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned - <i>Pag 7</i>
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions - <i>Pag 7</i>
17			
18			
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how - <i>Pag 10</i>
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial
26			
27			

### Methods: Data collection, management, and analysis

28			
29			
30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol
36			
37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol
46			
47			
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods		Reference to where other details of the statistical analysis plan can be
50			found, if not in the protocol
51			
52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses)
54			
55		20c	Definition of analysis population relating to protocol non-adherence
56			(eg, as randomised analysis), and any statistical methods to handle
57			missing data (eg, multiple imputation)
58			
59			
60			



## Methods: Monitoring

- 1  
2  
3  
4 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role  
5 and reporting structure; statement of whether it is independent from  
6 the sponsor and competing interests; and reference to where further  
7 details about its charter can be found, if not in the protocol.  
8 Alternatively, an explanation of why a DMC is not needed - *Pag 10*  
9  
10  
11 21b Description of any interim analyses and stopping guidelines, including  
12 who will have access to these interim results and make the final  
13 decision to terminate the trial - *Pag 10*  
14  
15 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and  
16 spontaneously reported adverse events and other unintended effects  
17 of trial interventions or trial conduct - *Pag 10*  
18  
19 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and  
20 whether the process will be independent from investigators and the  
21 sponsor  
22  
23

## Ethics and dissemination

- 24  
25  
26 Research ethics 24 Plans for seeking research ethics committee/institutional review board  
27 approval (REC/IRB) approval - *Pag 11*  
28  
29 Protocol 25 Plans for communicating important protocol modifications (eg,  
30 amendments changes to eligibility criteria, outcomes, analyses) to relevant parties  
31 (eg, investigators, REC/IRBs, trial participants, trial registries, journals,  
32 regulators)  
33  
34  
35 Consent or assent 26a Who will obtain informed consent or assent from potential trial  
36 participants or authorised surrogates, and how (see Item 32)  
37  
38 26b Additional consent provisions for collection and use of participant data  
39 and biological specimens in ancillary studies, if applicable - *No*  
40 *applicable*  
41  
42  
43 Confidentiality 27 How personal information about potential and enrolled participants will  
44 be collected, shared, and maintained in order to protect confidentiality  
45 before, during, and after the trial - *Pag 10-11*  
46  
47  
48 Declaration of 28 Financial and other competing interests for principal investigators for  
49 interests the overall trial and each study site - *Pag 13*  
50  
51 Access to data 29 Statement of who will have access to the final trial dataset, and  
52 disclosure of contractual agreements that limit such access for  
53 investigators - *Pag 10*  
54  
55 Ancillary and 30 Provisions, if any, for ancillary and post-trial care, and for  
56 post-trial care compensation to those who suffer harm from trial participation  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15
- |                         |     |   |
|-------------------------|-----|---|
| Dissemination<br>policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions - <i>Pag 12</i> |
|                         | 31b | Authorship eligibility guidelines and any intended use of professional writers - <i>Pag 12</i>  |
|                         | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code - <i>Pag 12</i>   |

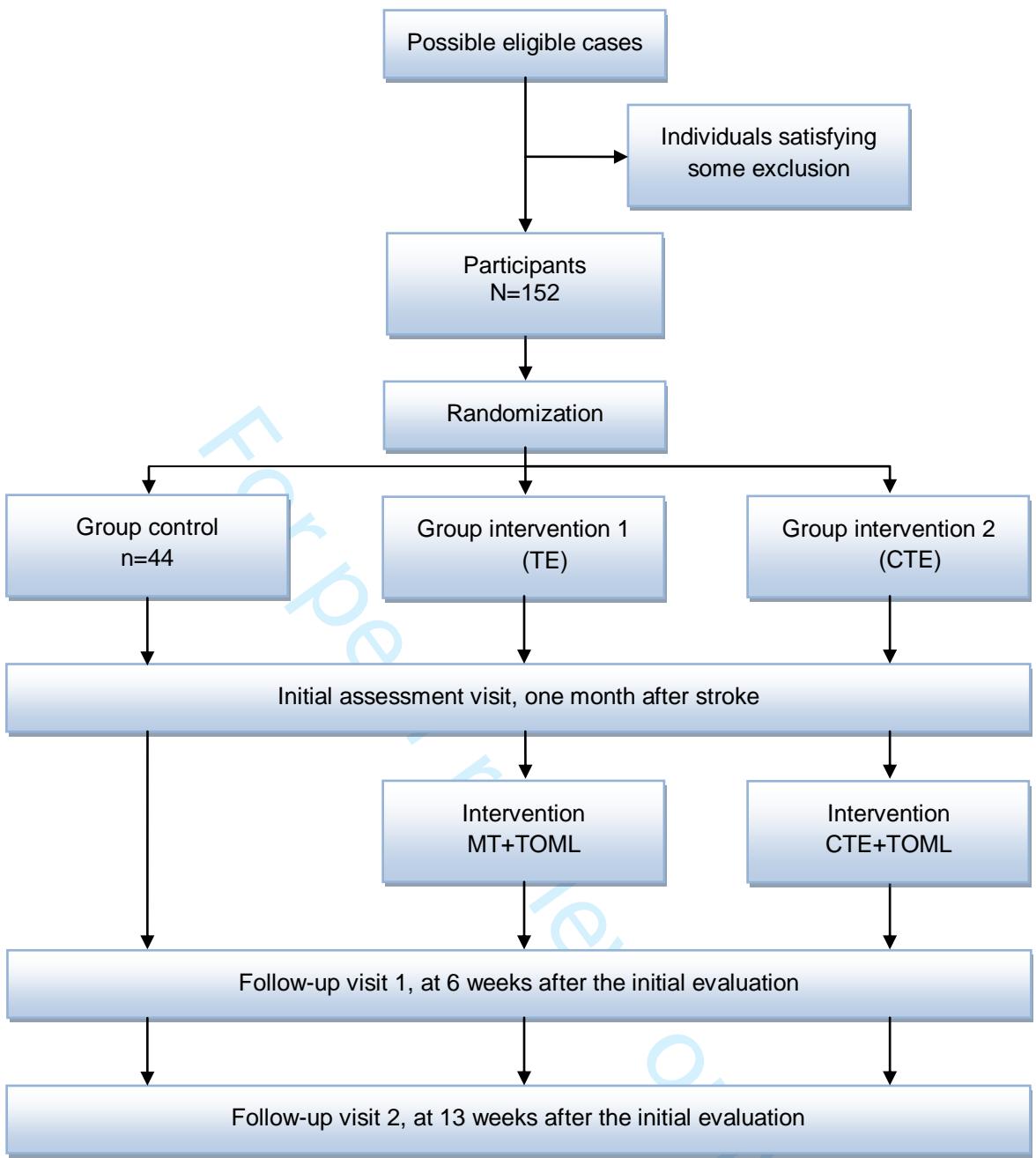
## 16 Appendices

- 17  
18  
19  
20  
21  
22  
23  
24
- |                               |    |  |
|-------------------------------|----|--|
| Informed consent<br>materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates - <i>Available</i>  |
| Biological<br>specimens       | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

---

25 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013  
26 Explanation & Elaboration for important clarification on the items. Amendments to the  
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT  
28 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)"  
29 license.  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Graph 1: Study flow chart.

# BMJ Open

**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.**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035768.R1
Article Type:	Protocol
Date Submitted by the Author:	27-Jun-2020
Complete List of Authors:	Gonzalez Santos, Josefa; University of Burgos, Health Sciences Soto-Camara, Raul; University of Burgos, Health Sciences Rodriguez-Fernández, Paula; University of Burgos, Health Sciences Jimenez-Barrios, Maria; University of Burgos, Health Sciences Gonzalez-Bernal, Jeronimo; University of Burgos, Health Sciences Collazo-Riobo, Carla ; University of Burgos, Health Sciences Jahouh, Maha; Universidad de Burgos, Health Sciences Bravo-Anguiano, Yolanda; Universitary Hospital of Burgos, Neurology Trejo-Gabriel-Galan, Jose M; Universitary Hospital of Burgos, Neurology
<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	NEUROLOGY, Stroke < NEUROLOGY, REHABILITATION MEDICINE

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

**TITLE:** 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.

**AUTHORS:**

- Josefa Gonzalez-Santos, PhD.<sup>1</sup>
- Raul Soto-Camara, MSN, PhD.<sup>1-2</sup>
- Paula Rodriguez-Fernandez, OT.<sup>1</sup>
- Maria Jimenez-Barrios, OT.<sup>1</sup>
- Jeronimo Gonzalez-Bernal, PhD.<sup>1</sup>
- Carla Collazo-Riobo, OT.<sup>1</sup>
- Maha Jahouh, OT.<sup>1</sup>
- Yolanda Bravo-Anguiano, MD, Neurologist.<sup>3</sup>
- Jose M Trejo-Gabriel-Galán, MD, Neurologist, Phd.<sup>3</sup>

**AUTHOR AFFILIATIONS:**

- Department of Health Sciences, University of Burgos, Spain.
- Emergency Medical Service, Health Service of Castilla y León, Burgos, Spain.
- Neurology Department, University Hospital of Burgos, Spain.

**CORRESPONDENCE AUTHORS:**

Raúl Soto-Cámara

Department of Health Sciences, University of Burgos, Spain. Paseo de los Comentadores s/n  
09001 - Burgos (Spain)

E-mail: [rscamara@ubu.es](mailto:rscamara@ubu.es) Phone number: +34 669 56957

**WORD COUNT:** 4920

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60**ABSTRACT**

**Introduction:** Neuroplasticity is defined as the capacity of the brain to reorganize new neuronal pathways. 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. Home-based interventions are an appropriate alternative to promote independence and autonomy. 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.

**Methods and analysis:** This is a home-based, single-blind, controlled, randomized clinical trial with three parallel arms, including 154 patients with stroke aged above 18 years. The primary outcome will be the functionality of the affected upper extremity measured using the Fugl-Meyer assessment. Secondary variables will include cognitive performance, emotional state, quality of life, and activities of daily living. 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. 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).

**Ethics and dissemination:** This protocol has been approved by the Institutional Review Board (CEIm-2.134/2.019) and registered at ClinicalTrials.gov (NCT04163666). The results will be disseminated through an open-access peer-reviewed journals, conference presentation, broadcast media, and a presentation to stakeholders. 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.

**Keywords:** stroke, upper limb, neurorehabilitation, mirror therapy, therapeutic cognitive exercise, task-oriented motor learning, Perfetti method.





## 1 INTRODUCTION

2 The World Health Organization defines stroke as a clinical syndrome of vascular origin,  
3 characterized by the rapid development of signs of focal and, on occasions, overall neurologic  
4 deficit, lasting for more than 24 hs<sup>1</sup>.

5 Stroke requires urgent neurological assistance and is the principal cause of physical disability  
6 among adults<sup>2</sup>. It has been estimated that a third of stroke-affected people remain dependent on  
7 others for care because they have an affectation in performing activities in any domain of life,  
8 including Basic Activities of Daily Living (BADL) and Instrumental Activities of Daily Living  
9 (IADL)<sup>3</sup>, because of sensory-based motor disorders; perception disorders; language and  
10 communication problems; and emotional, psychological, and behavioral disorders<sup>4,5</sup>.

11 Weakness (hemiparesis) or paralysis (hemiplegia) on the opposite side of the injured side is the first  
12 sequela of stroke in 80% of the patients<sup>4,6</sup>. Severe hemiparesis of the upper extremities, classified  
13 according to the Brunnstrom scale between stages II and IV or II and V depending on the author  
14 who considers it, is the most frequent cause of functional disability<sup>7</sup>. It is defined as the  
15 modification in the ability to perform a normal level of muscular strength, including altered  
16 sensitivity, weakness, motor control, and spasticity. It limits the performance of Daily Living  
17 Activities (DLA), significantly affecting the quality of life of patients with stroke<sup>8-11</sup>. Studies have  
18 shown that functional deficits after stroke are determined by different factors, including the  
19 structural extent of the damage and the level of cortical stimulation during the active or passive  
20 movement of the affected extremity. This fact must be considered in patients with severe  
21 hemiparesis, as first, the motor impairment they present prevents or limits the performance of  
22 functionally relevant activities of the affected extremity, and second, severe hemiparesis is  
23 commonly accompanied by sensory deficits. Therefore, despite increasing the use of the affected  
24 extremity to perform activities in traditional therapies, activation at the cortical level remains very  
25 limited<sup>8-11</sup>.

26 In the stroke rehabilitation process, special attention must be provided for the recovery of functional  
27 and motor activities of the affected upper extremity, needed for performing ADL<sup>9</sup>. It typically  
28 commences with spontaneous recovery during the first month, followed by learning-assisted  
29 recovery during the next six months and slow recovery during the subsequent months. This can be  
30 achieved as recovery is even possible in the most chronic phases because of cerebral plasticity and  
31 motor-related sensory learning<sup>12-14</sup>. Most studies have shown the importance of both patient-  
32 centered interventions and the need to combine different techniques, thereby not centering the  
33 treatment on a single modality<sup>13,15</sup>.

1  
2  
3  
4 1 Home-based therapy programs for recovery after stroke significantly improve independence and  
5 2 participation in ADL. These programs reduce long-term dependency<sup>16,17</sup> and are at least as effective  
6 3 as hospital interventions<sup>18</sup>. Despite the limited number of studies reporting on specific home-based  
7 4 therapy programs for the functional recovery of the upper extremity following stroke<sup>16,19</sup>, people  
8 5 who receive interventions for improving the functionality and reducing deterioration in the upper  
9 6 extremities have been shown to be more independent and more likely to maintain these skills in the  
10 7 long term if they receive this kind of therapy service<sup>20</sup>. At home, patients are forced to face the real  
11 8 challenges of daily life; therefore, in addition to improving functional outcome and satisfaction<sup>21,22</sup>,  
12 9 this type of intervention reduces depression<sup>23</sup> and encourages motivation and generalization of  
13 10 learning<sup>24,25</sup>.

14 11 This study is designed to create a home-based therapy program for the functional recovery of the  
15 12 upper extremities using mirror therapy (MT) or cognitive therapeutic exercise (CTE) in  
16 13 combination with task-oriented training and to verify which of these two techniques is more  
17 14 effective in functional recovery and movement patterns of the upper extremities in patients with  
18 15 severe hemiparesis after a stroke.

### 16 17 **Mirror Therapy**

18 18 The objective of MT, developed by Ramachandran and Rogers-Ramachandran<sup>26</sup>, is to improve  
19 19 motor functions of the affected upper extremities. In this therapy, the patient is guided such that the  
20 20 attention is centered on the reflection of the healthy upper extremity in a mirror as if it was the  
21 21 affected one<sup>6</sup>. The observation of normal movements in the mirror provides positive visual feedback  
22 22 and increases the flow of proprioceptive information and activates the neurons and the premotor  
23 23 cortex, thus improving the functionality of the affected upper extremity<sup>27-29</sup>.

24 24 Numerous studies have shown the benefits of MT in the rehabilitation of motor functions of the  
25 25 upper extremity, the performance of ADL, and pain thresholds of patients with stroke<sup>27-34</sup>.  
26 26 However, Oliveira and Castro<sup>35</sup> did not observe considerable improvements in self care because of  
27 27 different limitations such as the short duration of the program, small sample size, and lack of  
28 28 randomization.

29 29 Factors such as age, cognitive capability, and finger-related motor functioning of the affected or  
30 30 dominant hand affect the degree of effectiveness of MT in patients with hemiparesis<sup>6</sup>. Therefore,  
31 31 the majority of studies have agreed on the need for further research in this area<sup>27-35</sup>.

## 1 **Cognitive Therapeutic Exercise**

2 The objective of CTE or the Perfetti method, a cognitive rehabilitation modality, is to achieve motor  
3 functions using afferent information of a proprioceptive and/or tactile type. The proprioceptive  
4 information received is associated with the recognition of the direction, distance, and shapes  
5 through the body. The information associated with touch refers to the recognition of characteristics  
6 that are deduced by touching the object. The problem raised while perceiving the information can  
7 only be solved if the nature, intensity, and characteristics of the contact made are recognized.  
8 Therefore, the exercises are based on what the patient needs to recognize in an object: surface,  
9 pressure, friction resistance, or weight<sup>36</sup>.

10 The patient is expected to bring attention to parts or specific characteristics of the body while  
11 solving a cognitive problem that is described by the therapist. The problem is presented to the  
12 patient as the preparation of a perceptive hypothesis in such a way that the patient consciously  
13 perceives the upper extremity in a manner that favors the re-learning of a motor action that has been  
14 lost by the nervous system<sup>37</sup>.

15 CTE has been effective in improving muscle strength, tactile sensorial discrimination and  
16 kinesthetics, the functionality of the upper hemiplegic or hemiparetic extremities, and the quality of  
17 life of patients after stroke<sup>38-41</sup>.

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

## 22 **Task-oriented training**

23 Task-oriented training is an effective method to promote and stimulate motor skills and neuronal  
24 plasticity in patients with injuries to the central nervous system (CNS). It included the screening of  
25 the patient to develop personal strategies for performing useful functional movements in different  
26 contexts and situations<sup>41</sup>. The paretic hemibody is trained under suitable conditions using specific,  
27 repetitive, and intensive tasks, which are crucial for the patient<sup>41-44</sup>. By actively participating in the  
28 rehabilitation process and intervening in the search and discovery of strategies, personal functional  
29 independence is improved, and the adaptation of the patient to the environment is assisted<sup>41</sup>. This  
30 rehabilitation method uses five strategies to teach and motivate the patient, who must adapt to the  
31 requirements of each task: verbal instructions, visual demonstrations, manual guide, reinforcement,  
32 and positive feedback, and its repetitive practice in different contexts<sup>41</sup>.

1  
2  
3  
4 1 Despite scarce scientific evidence in this field in the literature, it has been observed that therapies  
5 2 with task-oriented functions facilitate greater functional recovery of the upper extremities.  
6 3 Therefore, a therapeutic approach based on task-oriented training that stimulates the potential  
7 4 neuroplasticity of CNS combined with techniques such as MT and CTE is of greater use in  
8 5 improving the motor function than the approaches based on a specific or concrete technique<sup>41,43,45–</sup>  
9 6 <sup>46</sup>.

10  
11  
12  
13  
14  
15  
16 8 Thus, a comparative study between MT and CTE has been planned. Although moderate-quality  
17 9 evidence exists to suggest that both techniques are effective in neurorehabilitation, their  
18 10 comparative effectiveness, or the one that yields better results and maintenance over time is yet to  
19 11 be confirmed<sup>47</sup>. Therefore, the objective of this study is to evaluate which of these techniques  
20 12 combined with task-oriented training is more effective in functional recovery and movement  
21 13 patterns of the upper extremities in patients with severe hemiparesis after stroke.

## 22 16 **METHODS AND ANALYSIS**

### 23 17 **Design and setting**

24 18 This is a single-blinded, controlled, randomized clinical trial with three parallel arms (control,  
25 19 intervention 1, and intervention 2). Participants will be enrolled from January 1, 2020 until 18  
26 20 months. At the first visit, just one month after having suffered from stroke, patients will be  
27 21 determined to meet the inclusion criteria, and the initial evaluation will be performed for patients  
28 22 who meet the criteria. A postintervention visit after six weeks will be conducted, and a follow-up  
29 23 visit will be conducted six months after stroke to evaluate the progress of patients in the subacute  
30 24 phase of recovery.

### 31 26 **Study population**

32 27 The participants will be recruited at the point of discharge from the Neurological Service and Stroke  
33 28 Unit of the Burgos University Hospital (Spain) by means of consecutive sampling. This is the only  
34 29 third-level health center for the referral of patients with stroke in the region. All evaluation and  
35 30 follow-up visits and the development of the interventions will be carried out in the patient's home.  
36 31 All participants meeting the following inclusion criteria would be included in the study: patients of  
37 32 both sexes, those aged 18 years or above, those with a diagnosis of residual hemiparesis because of  
38 33 ischemic or hemorrhagic stroke, those whose movements of the affected upper extremities are  
39 40  
41 42  
43 44  
45 45  
46 46  
47 47  
48 48  
49 49  
50 50  
51 51  
52 52  
53 53  
54 54  
55 55  
56 56  
57 57  
58 58  
59 59  
60 60

1  
2  
3  
4 1 classified between stages II and IV on the Brunnstrom Scale<sup>48</sup>, and those with a score on the  
5 2 Montreal Cognitive Assessment (MoCA) scale<sup>49</sup> equal to or above 26. All participants will be  
6 3 required to sign an informed consent form. Participants presenting hemineglect, Wernicke's  
7 4 aphasia, mixed aphasia, and/or visual deficits (homonymous hemianopsia) will be excluded from  
8 5 the study, considering the diagnostic information provided by the clinical assessment of neurologist.  
9 6  
10 7  
11 8  
12 9  
13 10  
14 11  
15 12  
16 13  
17 14  
18 15  
19 16  
20 17  
21 18  
22 19  
23 20  
24 21  
25 22  
26 23  
27 24  
28 25  
29 26  
30 27  
31 28  
32 29

### 33 30 **Patient and public involvement**

34 31 The patients and the public will participate in the study design so that time and spaces necessary for  
35 32 the home-based intervention could be adapted according to their availability. Moreover, they will be  
36 33 part of the data collection process and will be informed of the results obtained. Participants may  
37 34 suggest changes related to the frequency and intensity of the sessions. The results will be  
38 35 disseminated through communications, including media, healthcare institutions, patients'  
39 36 associations for which collaborative agreements are in place, and during meetings organized for  
40 37 sharing information with the participants of the study.  
41 38  
42 39  
43 40  
44 41  
45 42  
46 43  
47 44  
48 45  
49 46  
50 47  
51 48  
52 49  
53 50  
54 51  
55 52  
56 53  
57 54  
58 55  
59 56  
60 57

### 58 58 **Estimation of the sample size**

59 59 The sample size has been estimated on the basis of the potential modification of the main variable,  
60 60 i.e., the functionality of the affected upper extremity. Given alpha and beta risks of 0.05 and 0.20,  
61 61 respectively, in bilateral contrast, 110 participants (55 per group) will be required to detect a  
62 62 minimum difference of 0.50 in the functionality of the affected upper extremity using the Fugl-  
63 63 Meyer Assessment (FMA) between the two groups. An additional 44 individuals will be needed for  
64 64 calculating the size of the spontaneous improvement group, which is estimated to occur in 20% of  
65 65 the cases<sup>48</sup>. A predicted dropout rate of 10% during follow-up has been considered.  
66 66  
67 67  
68 68  
69 69  
70 70  
71 71  
72 72  
73 73  
74 74  
75 75  
76 76  
77 77  
78 78  
79 79  
80 80

### 79 79 **Randomization**

81 80 Participants will be randomly assigned either to a control group (CG) or an intervention group (IG).  
82 81 An assignment sequence in masking clusters at a ratio of 1:1:1 will be centrally generated by an  
83 82 independent researcher using the Epidat 4.2 program before the inclusion of the participants.  
84 83  
85 84  
86 85  
87 86  
88 87  
89 88  
90 89  
91 90  
92 91  
93 92  
94 93  
95 94  
96 95  
97 96  
98 97  
99 98  
100 99

### 99 99 **Intervention**

101 100 The standard rehabilitation treatment for stroke will be used for all study participants. Participants  
102 101 included in the CG will not receive any additional treatment or therapy.  
103 102  
104 103  
105 104  
106 105  
107 106  
108 107  
109 108  
110 109  
111 110  
112 111  
113 112  
114 113  
115 114  
116 115  
117 116  
118 117  
119 118  
120 119  
121 120  
122 121  
123 122  
124 123  
125 124  
126 125  
127 126  
128 127  
129 128  
130 129  
131 130  
132 131  
133 132  
134 133  
135 134  
136 135  
137 136  
138 137  
139 138  
140 139  
141 140  
142 141  
143 142  
144 143  
145 144  
146 145  
147 146  
148 147  
149 148  
150 149  
151 150  
152 151  
153 152  
154 153  
155 154  
156 155  
157 156  
158 157  
159 158  
160 159  
161 160  
162 161  
163 162  
164 163  
165 164  
166 165  
167 166  
168 167  
169 168  
170 169  
171 170  
172 171  
173 172  
174 173  
175 174  
176 175  
177 176  
178 177  
179 178  
180 179  
181 180  
182 181  
183 182  
184 183  
185 184  
186 185  
187 186  
188 187  
189 188  
190 189  
191 190  
192 191  
193 192  
194 193  
195 194  
196 195  
197 196  
198 197  
199 198  
200 199  
201 200  
202 201  
203 202  
204 203  
205 204  
206 205  
207 206  
208 207  
209 208  
210 209  
211 210  
212 211  
213 212  
214 213  
215 214  
216 215  
217 216  
218 217  
219 218  
220 219  
221 220  
222 221  
223 222  
224 223  
225 224  
226 225  
227 226  
228 227  
229 228  
230 229  
231 230  
232 231  
233 232  
234 233  
235 234  
236 235  
237 236  
238 237  
239 238  
240 239  
241 240  
242 241  
243 242  
244 243  
245 244  
246 245  
247 246  
248 247  
249 248  
250 249  
251 250  
252 251  
253 252  
254 253  
255 254  
256 255  
257 256  
258 257  
259 258  
260 259  
261 260  
262 261  
263 262  
264 263  
265 264  
266 265  
267 266  
268 267  
269 268  
270 269  
271 270  
272 271  
273 272  
274 273  
275 274  
276 275  
277 276  
278 277  
279 278  
280 279  
281 280  
282 281  
283 282  
284 283  
285 284  
286 285  
287 286  
288 287  
289 288  
290 289  
291 290  
292 291  
293 292  
294 293  
295 294  
296 295  
297 296  
298 297  
299 298  
300 299  
301 300  
302 301  
303 302  
304 303  
305 304  
306 305  
307 306  
308 307  
309 308  
310 309  
311 310  
312 311  
313 312  
314 313  
315 314  
316 315  
317 316  
318 317  
319 318  
320 319  
321 320  
322 321  
323 322  
324 323  
325 324  
326 325  
327 326  
328 327  
329 328  
330 329  
331 330  
332 331  
333 332  
334 333  
335 334  
336 335  
337 336  
338 337  
339 338  
340 339  
341 340  
342 341  
343 342  
344 343  
345 344  
346 345  
347 346  
348 347  
349 348  
350 349  
351 350  
352 351  
353 352  
354 353  
355 354  
356 355  
357 356  
358 357  
359 358  
360 359  
361 360  
362 361  
363 362  
364 363  
365 364  
366 365  
367 366  
368 367  
369 368  
370 369  
371 370  
372 371  
373 372  
374 373  
375 374  
376 375  
377 376  
378 377  
379 378  
380 379  
381 380  
382 381  
383 382  
384 383  
385 384  
386 385  
387 386  
388 387  
389 388  
390 389  
391 390  
392 391  
393 392  
394 393  
395 394  
396 395  
397 396  
398 397  
399 398  
400 399  
401 400  
402 401  
403 402  
404 403  
405 404  
406 405  
407 406  
408 407  
409 408  
410 409  
411 410  
412 411  
413 412  
414 413  
415 414  
416 415  
417 416  
418 417  
419 418  
420 419  
421 420  
422 421  
423 422  
424 423  
425 424  
426 425  
427 426  
428 427  
429 428  
430 429  
431 430  
432 431  
433 432  
434 433  
435 434  
436 435  
437 436  
438 437  
439 438  
440 439  
441 440  
442 441  
443 442  
444 443  
445 444  
446 445  
447 446  
448 447  
449 448  
450 449  
451 450  
452 451  
453 452  
454 453  
455 454  
456 455  
457 456  
458 457  
459 458  
460 459  
461 460  
462 461  
463 462  
464 463  
465 464  
466 465  
467 466  
468 467  
469 468  
470 469  
471 470  
472 471  
473 472  
474 473  
475 474  
476 475  
477 476  
478 477  
479 478  
480 479  
481 480  
482 481  
483 482  
484 483  
485 484  
486 485  
487 486  
488 487  
489 488  
490 489  
491 490  
492 491  
493 492  
494 493  
495 494  
496 495  
497 496  
498 497  
499 498  
500 499  
501 500  
502 501  
503 502  
504 503  
505 504  
506 505  
507 506  
508 507  
509 508  
510 509  
511 510  
512 511  
513 512  
514 513  
515 514  
516 515  
517 516  
518 517  
519 518  
520 519  
521 520  
522 521  
523 522  
524 523  
525 524  
526 525  
527 526  
528 527  
529 528  
530 529  
531 530  
532 531  
533 532  
534 533  
535 534  
536 535  
537 536  
538 537  
539 538  
540 539  
541 540  
542 541  
543 542  
544 543  
545 544  
546 545  
547 546  
548 547  
549 548  
550 549  
551 550  
552 551  
553 552  
554 553  
555 554  
556 555  
557 556  
558 557  
559 558  
560 559  
561 560  
562 561  
563 562  
564 563  
565 564  
566 565  
567 566  
568 567  
569 568  
570 569  
571 570  
572 571  
573 572  
574 573  
575 574  
576 575  
577 576  
578 577  
579 578  
580 579  
581 580  
582 581  
583 582  
584 583  
585 584  
586 585  
587 586  
588 587  
589 588  
590 589  
591 590  
592 591  
593 592  
594 593  
595 594  
596 595  
597 596  
598 597  
599 598  
600 599  
601 600  
602 601  
603 602  
604 603  
605 604  
606 605  
607 606  
608 607  
609 608  
610 609  
611 610  
612 611  
613 612  
614 613  
615 614  
616 615  
617 616  
618 617  
619 618  
620 619  
621 620  
622 621  
623 622  
624 623  
625 624  
626 625  
627 626  
628 627  
629 628  
630 629  
631 630  
632 631  
633 632  
634 633  
635 634  
636 635  
637 636  
638 637  
639 638  
640 639  
641 640  
642 641  
643 642  
644 643  
645 644  
646 645  
647 646  
648 647  
649 648  
650 649  
651 650  
652 651  
653 652  
654 653  
655 654  
656 655  
657 656  
658 657  
659 658  
660 659  
661 660  
662 661  
663 662  
664 663  
665 664  
666 665  
667 666  
668 667  
669 668  
670 669  
671 670  
672 671  
673 672  
674 673  
675 674  
676 675  
677 676  
678 677  
679 678  
680 679  
681 680  
682 681  
683 682  
684 683  
685 684  
686 685  
687 686  
688 687  
689 688  
690 689  
691 690  
692 691  
693 692  
694 693  
695 694  
696 695  
697 696  
698 697  
699 698  
700 699  
701 700  
702 701  
703 702  
704 703  
705 704  
706 705  
707 706  
708 707  
709 708  
710 709  
711 710  
712 711  
713 712  
714 713  
715 714  
716 715  
717 716  
718 717  
719 718  
720 719  
721 720  
722 721  
723 722  
724 723  
725 724  
726 725  
727 726  
728 727  
729 728  
730 729  
731 730  
732 731  
733 732  
734 733  
735 734  
736 735  
737 736  
738 737  
739 738  
740 739  
741 740  
742 741  
743 742  
744 743  
745 744  
746 745  
747 746  
748 747  
749 748  
750 749  
751 750  
752 751  
753 752  
754 753  
755 754  
756 755  
757 756  
758 757  
759 758  
760 759  
761 760  
762 761  
763 762  
764 763  
765 764  
766 765  
767 766  
768 767  
769 768  
770 769  
771 770  
772 771  
773 772  
774 773  
775 774  
776 775  
777 776  
778 777  
779 778  
780 779  
781 780  
782 781  
783 782  
784 783  
785 784  
786 785  
787 786  
788 787  
789 788  
790 789  
791 790  
792 791  
793 792  
794 793  
795 794  
796 795  
797 796  
798 797  
799 798  
800 799  
801 800  
802 801  
803 802  
804 803  
805 804  
806 805  
807 806  
808 807  
809 808  
810 809  
811 810  
812 811  
813 812  
814 813  
815 814  
816 815  
817 816  
818 817  
819 818  
820 819  
821 820  
822 821  
823 822  
824 823  
825 824  
826 825  
827 826  
828 827  
829 828  
830 829  
831 830  
832 831  
833 832  
834 833  
835 834  
836 835  
837 836  
838 837  
839 838  
840 839  
841 840  
842 841  
843 842  
844 843  
845 844  
846 845  
847 846  
848 847  
849 848  
850 849  
851 850  
852 851  
853 852  
854 853  
855 854  
856 855  
857 856  
858 857  
859 858  
860 859  
861 860  
862 861  
863 862  
864 863  
865 864  
866 865  
867 866  
868 867  
869 868  
870 869  
871 870  
872 871  
873 872  
874 873  
875 874  
876 875  
877 876  
878 877  
879 878  
880 879  
881 880  
882 881  
883 882  
884 883  
885 884  
886 885  
887 886  
888 887  
889 888  
890 889  
891 890  
892 891  
893 892  
894 893  
895 894  
896 895  
897 896  
898 897  
899 898  
900 899  
901 900  
902 901  
903 902  
904 903  
905 904  
906 905  
907 906  
908 907  
909 908  
910 909  
911 910  
912 911  
913 912  
914 913  
915 914  
916 915  
917 916  
918 917  
919 918  
920 919  
921 920  
922 921  
923 922  
924 923  
925 924  
926 925  
927 926  
928 927  
929 928  
930 929  
931 930  
932 931  
933 932  
934 933  
935 934  
936 935  
937 936  
938 937  
939 938  
940 939  
941 940  
942 941  
943 942  
944 943  
945 944  
946 945  
947 946  
948 947  
949 948  
950 949  
951 950  
952 951  
953 952  
954 953  
955 954  
956 955  
957 956  
958 957  
959 958  
960 959  
961 960  
962 961  
963 962  
964 963  
965 964  
966 965  
967 966  
968 967  
969 968  
970 969  
971 970  
972 971  
973 972  
974 973  
975 974  
976 975  
977 976  
978 977  
979 978  
980 979  
981 980  
982 981  
983 982  
984 983  
985 984  
986 985  
987 986  
988 987  
989 988  
990 989  
991 990  
992 991  
993 992  
994 993  
995 994  
996 995  
997 996  
998 997  
999 998  
1000 999  
1001 1000  
1002 1001  
1003 1002  
1004 1003  
1005 1004  
1006 1005  
1007 1006  
1008 1007  
1009 1008  
1010 1009  
1011 1010  
1012 1011  
1013 1012  
1014 1013  
1015 1014  
1016 1015  
1017 1016  
1018 1017  
1019 1018  
1020 1019  
1021 1020  
1022 1021  
1023 1022  
1024 1023  
1025 1024  
1026 1025  
1027 1026  
1028 1027  
1029 1028  
1030 1029  
1031 1030  
1032 1031  
1033 1032  
1034 1033  
1035 1034  
1036 1035  
1037 1036  
1038 1037  
1039 1038  
1040 1039  
1041 1040  
1042 1041  
1043 1042  
1044 1043  
1045 1044  
1046 1045  
1047 1046  
1048 1047  
1049 1048  
1050 1049  
1051 1050  
1052 1051  
1053 1052  
1054 1053  
1055 1054  
1056 1055  
1057 1056  
1058 1057  
1059 1058  
1060 1059  
1061 1060  
1062 1061  
1063 1062  
1064 1063  
1065 1064  
1066 1065  
1067 1066  
1068 1067  
1069 1068  
1070 1069  
1071 1070  
1072 1071  
1073 1072  
1074 1073  
1075 1074  
1076 1075  
1077 1076  
1078 1077  
1079 1078  
1080 1079  
1081 1080  
1082 1081  
1083 1082  
1084 1083  
1085 1084  
1086 1085  
1087 1086  
1088 1087  
1089 1088  
1090 1089  
1091 1090  
1092 1091  
1093 1092  
1094 1093  
1095 1094  
1096 1095  
1097 1096  
1098 1097  
1099 1098  
1100 1099  
1101 1100  
1102 1101  
1103 1102  
1104 1103  
1105 1104  
1106 1105  
1107 1106  
1108 1107  
1109 1108  
1110 1109  
1111 1110  
1112 1111  
1113 1112  
1114 1113  
1115 1114  
1116 1115  
1117 1116  
1118 1117  
1119 1118  
1120 1119  
1121 1120  
1122 1121  
1123 1122  
1124 1123  
1125 1124  
1126 1125  
1127 1126  
1128 1127  
1129 1128  
1130 1129  
1131 1130  
1132 1131  
1133 1132  
1134 1133  
1135 1134  
1136 1135  
1137 1136  
1138 1137  
1139 1138  
1140 1139  
1141 1140  
1142 1141  
1143 1142  
1144 1143  
1145 1144  
1146 1145  
1147 1146  
1148 1147  
1149 1148  
1150 1149  
1151 1150  
1152 1151  
1153 1152  
1154 1153  
1155 1154  
1156 1155  
1157 1156  
1158 1157  
1159 1158  
1160 1159  
1161 1160  
1162 1161  
1163 1162  
1164 1163  
1165 1164  
1166 1165  
1167 1166  
1168 1167  
1169 1168  
1170 1169  
1171 1170  
1172 1171  
1173 1172  
1174 1173  
1175 1174  
1176 1175  
1177 1176  
1178 1177  
1179 1178  
1180 1179  
1181 1180  
1182 1181  
1183 1182  
1184 1183  
1185 1184  
1186 1185  
1187 1186  
1188 1187  
1189 1188  
1190 1189  
1191 1190  
1192 1191  
1193 1192  
1194 1193  
1195 1194  
1196 1195  
1197 1196  
1198 1197  
1199 1198  
1200 1199  
1201 1200  
1202 1201  
1203 1202  
1204 1203  
1205 1204  
1206 1205  
1207 1206  
1208 1207  
1209 1208  
1210 1209  
1211 1210  
1212 1211  
1213 1212  
1214 1213  
1215 1214  
1216 1215  
1217 1216  
1218 1217  
1219 1218  
1220 1219  
1221 1220  
1222 1221  
1223 1222  
1224 1223  
1225 1224  
1226 1225  
1227 1226  
1228 1227  
1229 1228  
1230 1229  
1231 1230  
1232 1231  
1233 1232  
1234 1233  
1235 1234  
1236 1235  
1237 1236  
1238 1237  
1239 1238  
1240 1239  
1241 1240  
12

1  
2  
3  
4 1 IG<sup>-1</sup> will receive an additional treatment of MT with task-oriented training, whereas IG<sup>-2</sup> will  
5 2 receive CTE with task-oriented training. In both groups, the interventions will begin at the  
6 3 participant's home during a period of six weeks (30 days), including 60-minute sessions, 30 min of  
7 4 which will be for MT or CTE, and the remaining 30 min will be for task-oriented training.

#### 10 5 *Task-oriented training*

12 6 Task-oriented training will be presented sequentially in a structured manner along with their  
13 7 specific characteristics, which would vary from one session to another to facilitate in their  
14 8 application in daily life. The complex activities will be divided into simpler tasks for easy learning.  
15 9 Verbal instructions and/or presentations will be provided, gradually decreasing the support. Every  
16 10 day of the week will be dedicated to a different BADL among the following: diet (preparing and  
17 11 organizing food, as well as time taken to eat), clothing (upper and lower extremities), and personal  
18 12 hygiene (brushing teeth, combing hair, and shaving or applying makeup). There will be short  
19 13 resting periods, and the difficulty of tasks will be progressively increased to assist carry over. The  
20 14 last week will be dedicated to tasks and BADL that the patient requests and can be performed at  
21 15 home<sup>50</sup>.

#### 29 16 *Mirror Therapy*

31 17 In the MT, the patient will be seated on an ordinary chair, with their forearms resting on a table. A  
32 18 mirror will be placed between both the arms at a right angle to the torso. The affected extremity  
33 19 must be placed behind the mirror, in a comfortable position, in such a way that the patient cannot  
34 20 see it. The healthy extremity must be placed in a position as similar as possible to the affected  
35 21 extremity so that it completely reflects in the mirror with no distortion of the image. Any object or  
36 22 symbol that can identify the healthy extremity must be removed or covered up (Figure 1).

41 23 MT can be used in three different modes. In the first mode, the patient tries to imitate the movement  
42 24 of the healthy hand with the affected hand in a synchronized way. In the second mode, the patient  
43 25 only imagines that the reflected movement of the healthy hand is being performed by his affected  
44 26 hand. In the third mode, the therapist assists patient's affected hand to imitate the movement  
45 27 performed by the healthy hand. Considering these modes, first simple exercises without objects  
46 28 were performed with the healthy hand while imagining the same movement with the affected hand;  
47 29 then, the same movements are performed by the affected hand with the help of the therapist<sup>51,52</sup>.

53 30 Simple movements without any objects will be performed during the first 10 sessions, and then,  
54 31 simple movements using objects will be performed in the following 10 sessions. Moreover,  
55 32 movements of greater complexity with objects will be included in the last 10 sessions. To be more  
56 33 specific, the patient will complete movements with a healthy hand throughout the first three groups  
57  
58  
59  
60

1  
2  
3  
4 1 of 10 sessions and will try to imagine them with the affected hand (mode). Those movements will  
5 2 be assisted by a therapist in the three subsequent sessions (mode), whereas the patient will try to  
6 3 imitate the movements of the healthy hand by the affected hand throughout the last four sessions  
7 4 (mode). All the exercises will have to be completed slowly and repeated at least 15 times. The  
8 5 activities and their levels of complexity will be adjusted as per the limitations and capabilities of  
9 6 each patient<sup>51,52</sup>.

### 14 7 *Cognitive Therapeutic Exercise*

15 8 The cognitive therapeutic exercises (CTE) are classified according to multiple criteria in three  
16 9 different modalities: first, second, and third grades. All patients will begin performing the first-  
17 10 grade exercises until they regain the ability to control the reaction to stretching to graduate intensity,  
18 11 time, and spatiality. Once the patient can successfully perform the first-degree exercises, control the  
19 12 reactions to stretching in a sufficiently automated way, and frequently perform selective movements  
20 13 of the fingers and other body segments, the second-degree exercises are performed<sup>39,53</sup>.

21 14 Finally, third-degree exercises are performed through which the patient learns to adapt movements  
22 15 to the proposed perceptual hypothesis after the patient has managed to automate the control of  
23 16 abnormal motor behaviors with the second-degree exercises. The criteria that must be considered to  
24 17 establish correct programming of the exercises depend on the configuration of the trajectories that  
25 18 are requested from the patient and on the intensity of the contractions that must be activated in the  
26 19 segments that execute them<sup>36</sup>.

27 20 In the first-degree modality, the aim is to control the exaggerated reaction to stretching (commonly  
28 21 known as spasticity) and overcome the sensitivity deficit, where the therapist performs the patient's  
29 22 movements. These exercises are not entirely considered passive as they require the patient's  
30 23 attention at all times. Moreover, in the second-degree modality, the objective is to control abnormal  
31 24 irradiation (involuntary activation of muscle groups). In this case, the movements are performed by  
32 25 the patient with the minimum necessary help from the therapist. These exercises include tactile,  
33 26 kinesthetic, weight, grip, and friction input. This modality will be introduced in combination with  
34 27 the first-degree exercises once the patient has acquired a certain degree of control over the  
35 28 recruitment of motor units. Finally, in the third-grade modality, the control of voluntary movements  
36 29 and the decisions on their fragmentation, variability, and adaptation will be emphasized, with the  
37 30 aim of achieving perfect automation of movements wherein the patient is totally active and does not  
38 31 need any type of help from the therapist. The information is received through the same method as in  
39 32 the previous modality<sup>36,53,54</sup>.

1  
2  
3  
4 1 For its application, the CTE always proposes each exercise in the same structure such that first, a  
5 2 cognitive problem is proposed, then a perceptual hypothesis (feedforward) is activated to solve the  
6 3 problem, and finally, a comparison process occurs between the previous and sensory information  
7 4 (feedback) that the patient receives during the therapeutic exercise<sup>53</sup>. Before starting the activity, the  
8 5 patient is shown different materials or subsidies using which the exercise is performed. During this  
9 6 time, the patient must recognize the possible strategies that help in solving the problem by  
10 7 collecting information through his body<sup>53</sup>. Therefore, the elements present in any exercise of the  
11 8 present technique are the cognitive problem, perceptual hypothesis, and verification of that  
12 9 hypothesis.

13 10 For example, the therapist shows the patient three two-dimensional figures (triangle, circle, and  
14 11 square), allowing the patient to observe and touch them. Then, the patient closes his eyes and  
15 12 touches the figures with his fingertips (guided or not by the professional), and with the information  
16 13 received through the body, the patients should recognize the figure.

## 17 14

### 18 15 **Procedure**

19 16 An initial evaluation visit will be completed in the fourth week after stroke, and a postintervention  
20 17 visit at week 6 will be performed. A follow-up visit will occur six months poststroke to evaluate the  
21 18 progress of patients with stroke in the subacute phase of recovery. Both IG and CG will undergo all  
22 19 the evaluations. Their state will be assessed using different instruments and questionnaires in all  
23 20 visits.

24 21 All participants included in the IG will receive 30 treatment sessions, distributed between the initial  
25 22 evaluation and the first follow-up visit (Figure 2).

### 26 23

### 27 24 **Primary and secondary endpoints**

28 25 The primary outcome will be an improvement in the functionality of the affected upper extremity.  
29 26 The secondary variables will include cognitive performance, emotional state, quality of life, and  
30 27 performance of ADL. The primary and secondary endpoints will be evaluated at six months  
31 28 poststroke through the use of questionnaires, previously validated for the Spanish population.

#### 32 29 *The functionality of the affected upper extremity*

33 30 To perform a thorough assessment, different motor deficit components of the affected upper  
34 31 extremity will be evaluated using the FMA, which will be combined with four other scales:

- 35 32 • The FMA<sup>55</sup>, which assesses motor functioning, passive articular mobility, articular pain,  
36 33 coordination, and balance;



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1 • The Action Research Arm Test<sup>56</sup>, which measures the functionality of the upper extremity;
- 2 • The Motor Activity Log 30<sup>56</sup>, which assesses the quantity (subscale CU) and quality (CM scale)
- 3 of use of hand and arms during the performance of ADL;
- 4 • The Block and Box Test<sup>57</sup>, which assesses the manipulative value of the hand; and
- 5 • The Modified Ashworth Scale<sup>58</sup>, which measures the spasticity of all the movements of the
- 6 different joints of the upper extremity: shoulder (flexion, extension, abduction, adduction, and
- 7 internal and external rotation); elbow (flexion, extension, pronation, and supination); wrist
- 8 (flexion, extension, and ulnar and radial deviation); distal and proximal metacarpophalangeal
- 9 and interphalangeal (flexion and extension); the second to fifth fingers (abduction and
- 10 adduction); and thumb (flexion, extension, abduction, and adduction).

### 11 *Cognitive performance*

12 The cognitive performance will be evaluated using the MoCA scale<sup>49</sup>, distributed into seven  
13 different cognitive domains: visuospatial executive capacity; denomination; language attention;  
14 abstraction; learning; and deferred learning, recall, and orientation.

### 15 *Emotional state and quality of life*

16 Emotional state and quality of life will be evaluated using the Escala de Calidad de Vida para el  
17 Ictus (Scale of PostStroke Quality of Life)<sup>59</sup>, which comprises 38 items grouped into eight domains:  
18 physical state, communication, cognition, emotions, feelings, BADL, common ADL, and socio-  
19 family functioning.

### 20 *Performance of ADL*

21 BADL will be evaluated using the Functional Independence Measure and its extension, the  
22 Functional Assessment Measure, designed specifically for patients with cerebral damage<sup>60</sup>. The 30  
23 items in this instrument are used to assess the self-care tasks inherent to ADL, motor, cognitive, and  
24 behavioral functions and communicative and functional behavior in the community.

25 The IADL will be evaluated using the Lawton-Brody index<sup>61</sup>. It assesses the capability to develop  
26 tasks involving the handling of everyday utensils and day-to-day social activities, including  
27 telephone use, shopping, preparing meals, household work, washing clothes, transport use,  
28 responsibility for medication administration, and management of economic affairs.

### 29 *Other measures/covariables*

30 The following variables will be evaluated to control the possible predictive or confusion factors:  
31 age, sex, type of stroke, affected cerebral hemisphere, and stroke severity, quantified by the  
32 National Institute Health Stroke Scale<sup>62</sup>.

## **Data collection, data management, and follow-up procedure**

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. Each participant will be assigned a unique intervention code for this study. All the assessments would be entered into a safe and secure data collection notebook. A database would be created using the SPSS software version 25.00 (IBM SOSS Inc, Chicago, IL, USA), accessible only to the research team members and the ones involved in the statistical analysis of the study. A researcher on a weekly basis will monitor the inclusion of new patients, debugging, testing, checking of databases, and adaption of protocol procedures. Double entry of data will be performed to maintain a low error rate.

### **Blinding strategy**

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.

### **Statistical analysis**

#### *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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1 analysis will be performed using the SPSS software version 25.0 (IBM SOSS Inc, Chicago, IL,  
2 USA).

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

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

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

### 11 *Analysis by subgroups*

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

### 15 *Secondary analysis*

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

## 20 **ETHICS AND DISSEMINATION**

### 21 **Ethical considerations**

22 The study has been approved by the Clinical Research Ethics Committee of the Health Area of  
23 Burgos and Soria (Spain) in June 2019 (CEIm 2.134/2.019). A SPIRIT declaration checklist is  
24 available for this protocol. The clinical test has been registered at ClinicalTrials.gov with identifier  
25 no. NCT04163666.

26 In accordance with the Helsinki Declaration, prior informed consent will be obtained from the  
27 individuals who voluntarily decide to participate. They will be informed of the objectives, risks, and  
28 benefits of the assessments, as well as the interventions that will be used. None of the activities  
29 imply additional risks to the life of the participants. At all times, the confidentiality of the data will  
30 be guaranteed in accordance with the current legislation.

## 1 **Dissemination plan**

2 The dissemination of results will be as per the recommendations mentioned in the CONSORT  
3 declaration. This study will be published in open access peer-reviewed scientific journals, so as to  
4 acquire the highest possible visibility for the study. At least two publications are expected to be  
5 completed, one of the results of the primary outcome (functionality of the upper extremity) and the  
6 other on the secondary results. The results will be disseminated through communications, including  
7 media and social networks, as well as at international and national scientific conferences and  
8 seminars. Similarly, a doctoral thesis based on the content of this project will be developed.

## 9 **DISCUSSION**

10 At present, a number of rehabilitative methods exist based on the principle of cerebral plasticity.  
11 Among these, MT and CTE promote the recovery of the affected upper extremity.

12 Various clinical trials have demonstrated that MT is an effective treatment for the recovery of the  
13 upper extremity in patients with subacute stroke<sup>27-34</sup>. Vandana et al.<sup>48</sup> evaluated the effects of MT  
14 on motor recovery of the upper extremities, spasticity, and hand-related functionality of patients  
15 with subacute stroke and severe hemiparesis (stages II to IV of the Brunnstrom scale). Moreover, a  
16 greater improvement in the scores of the Brunnstrom stages for the hand and upper extremity was  
17 observed in the MT group than the conventional therapy group. Ayra et al.<sup>63</sup> evaluated a specific  
18 task-based neurorehabilitation therapy among patients with subacute stroke with severe hemiparesis  
19 (stages II to V of the Brunnstrom scale) and showed that there were greater improvements in  
20 performing activities with this method than with any other conventional method. Lisalde-  
21 Rodríguez<sup>64</sup> demonstrated that MT combined with conventional therapy was effective in improving  
22 the motor function of the upper paretic extremity but not the overall functionality of the patient. In  
23 another study, MT combined with task-oriented training within the same treatment session showed  
24 statistically significant results in the functionality of the upper extremity and the performance of  
25 ADL in the patient<sup>43</sup>. Kim et al.<sup>12</sup> involving 25 patients with stroke confirmed the effectiveness of  
26 an intervention with MT combined with task-oriented training in comparison to conventional  
27 therapy. MT combined with task-oriented training is the most effective method in the rehabilitation  
28 of the affected upper extremity functionality and performance of ADL.

29 Despite having demonstrated the effectiveness of CTE in executing simple motor activities such as  
30 cylindrical grip, it lacks evidence on its repercussions on the recovery of distal functions of greater  
31 complexity among patients with the affected upper extremities following a stroke ictus<sup>38</sup>.

1  
2  
3  
4 1 Although this study relates both the treatment techniques, it presents significant limitations such as  
5 2 lack of specificity on the level of deficit affecting the upper extremity, sample size, and the control  
6 3 groups. It is necessary to determine the correct execution and description of activities, processes,  
7 4 and exercises for their development and, similarly, to validate future investigations on a scientific  
8 5 basis. No studies until date have demonstrated which out of the two techniques is the most effective  
9 6 in achieving functional recovery of the affected upper extremity.

10 7 This study will provide novel and useful results for the development of poststroke rehabilitation  
11 8 strategies. The intervention may provide implications for the preparation of evidence-based  
12 9 recommendations, practical clinical guidelines, and continuous quality improvement programs for  
13 10 patients with severe hemiparesis after stroke.

14 11 The relevant information will be obtained about the functionality of the upper extremity of patients  
15 12 with severe hemiparesis after the practice of a more intensive therapy that combines two types of  
16 13 neurorehabilitation approaches.

17 14 The sample size of this study helps in understanding the relevant aspects of conducting future  
18 15 studies, and it will also provide greater confidence and credibility regarding the benefits of these  
19 16 neurorehabilitation approaches.

20 17 Until now, the effectiveness of both techniques is known; however, this study will facilitate the  
21 18 professional to select the technique that should be implemented in his rehabilitation to achieve the  
22 19 best possible results.

23 20 Lastly, the fact that it is a home-based intervention that combines MT and CTE with task-oriented  
24 21 training will help us to discover if these factors influence the transfer of the movement patterns  
25 22 learned during the different interventions to the execution of ADL.

26 23  
27 24 **Authors' contributions:** JGS, PRF, MJB, CCR and MJ devised the design of the study. JGB, PRF,  
28 25 MJB and RSC prepared and developed the protocol study. JGS, JGB and RSC provided  
29 26 methodological assistance and statistical assessment. YBA and JMTGG provided a critical review  
30 27 of the paper. All the authors have read and accepted the final version of the protocol.

31 28  
32 29 **Funding:** This research will receive no specific grant from any funding agency in the public,  
33 30 commercial or not-for-profit sectors.

34 31  
35 32 **Competing interests:** None declared  
36 33  
37 34  
38 35  
39 36  
40 37  
41 38  
42 39  
43 40  
44 41  
45 42  
46 43  
47 44  
48 45  
49 46  
50 47  
51 48  
52 49  
53 50  
54 51  
55 52  
56 53  
57 54  
58 55  
59 56  
60 57

1  
2  
3  
4 1 **Legends of figures:**

5 2 1. **Figure 1:** In the intervention set up for mirror therapy, the participant looks at the reflection of  
6  
7 3 the unaffected hand in the mirror as if it was the affected hand.

8  
9 4 2. **Figure 2:** Study flow chart.  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 1 2 3 4 **REFERENCES**

- 5 2 1. Hetano S. Experience from a multicentre stroke register: a preliminary report. *Bull World*  
6 3 *Health Organ.* 1976; 54(5): 541-53.
- 7 4 2. Organización Mundial de la Salud (OMS). Enfermedades cardiovasculares [sede Web]. Who;  
8 5 2017. Enfermedades cardiovasculares. Available at: [https://www.who.int/es/news-room/fact-](https://www.who.int/es/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds))  
9 6 [sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/es/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds))
- 10 7 3. Legg L, Drummond A, Langhorne P. Occupational therapy for patients with problems in  
11 8 activities of daily living after stroke. *Cochrane Database Syst Rev.* 2006; 4: CD 003585. Doi:  
12 9 10.1002/14651858.CD003585.pub2.
- 13 10 4. Polonio López B, Romero Ayuso DM. Terapia Ocupacional aplicada al daño cerebral  
14 11 adquirido. Madrid: Editorial Médica Panamericana, SA; 2010.
- 15 12 5. Ministerio de Sanidad y Política Social. Guía de Práctica Clínica para el manejo de pacientes  
16 13 con ictus en Atención Primaria. Madrid; 2009.
- 17 14 6. Brunetti M, Morkisch N, Fritsch C, Mehnert J, Steinbrink J, Niedeggen M et al. Potential  
18 15 determinants of efficacy of mirror therapy in stroke patients. A pilot study. *Restor Neurol*  
19 16 *Neurosci.* 2015; 33(4): 421-34. Doi: 10.3233 / RNN-140421.
- 20 17 7. Dohle C, Püllen J, Nakaten A, Küst J, Rietz C, Karbe H et al. Mirror therapy promotes  
21 18 recovery from severe. A randomized controlled trial. *Neurorehabil Neural Repair.* 2009; 23(3):  
22 19 209-17. Doi: 10.1177/1545968308324786
- 23 20 8. Fernández-Gómez E, Sánchez-Cabeza A. Motor imagery: a systematic review of its  
24 21 effectiveness in the rehabilitation of the upper limb following a stroke. *Rev Neurol.* 2018;  
25 22 66(5): 137-46. Doi: doi.org/10.33588/rn.6605.2017394
- 26 23 9. Wist S, Clivaz J, Sattelmayer M. Muscle strengthening for hemiparesis after stroke: A meta-  
27 24 analysis. *Ann Phys Rehabil Med.* 2016; 59(2): 114-24. Doi: 10.1016/j.rehab.2016.02.001
- 28 25 10. Hara T, Abo M, Kakita K, Masuda T, Yamazaki R. Does a combined intervention program of  
29 26 repetitive transcranial magnetic stimulation and intensive occupational therapy affect cognitive  
30 27 function in patients with post-stroke upper limb hemiparesis? *Neural Regen Res.* 2016; 11(12):  
31 28 1932-9. Doi: 10.4103/1673-5374.197134
- 32 29 11. Kakuda W, Abo M, Sasanuma J, Shimizu M, Okamoto T, Kimura C et al. Combination  
33 30 protocol of low-frequency rTMS and intensive occupational therapy for post-stroke upper limb  
34 31 hemiparesis: a 6-year experience of more than 1700 japanese patients. *Transl Stroke Res.* 2016;  
35 32 7(3): 172-9. Doi: 10.1007/s12975-016-0456-8
- 36 33 12. Kim K, Lee S, Kim D, Lee K, Kim Y. Effects of mirror therapy combined with motor tasks on  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 1 upper extremity function and activities daily living of stroke patients. *J Phys Ther Sci.* 2016;  
5 2 28(2): 483-7. Doi: 10.1589/jpts.28.483  
6  
7 3 13. Schaechter JD. Motor rehabilitation and brain plasticity after hemiparetic stroke. *Prog*  
8 *Neurobiol.* 2004; 73(1): 61-72. Doi: 10.1016/j.pneurobio.2004.04.001  
9 4  
10 5 14. Murie-Fernández M, Irimia P, Martínez-Vila E, John-Meyerc M, Teasella R. Neuro-  
11 6 rehabilitation after stroke. *Rev Neurol.* 2010; 25(3): 189-96. Doi: 10.1016/S0213-  
12 7 4853(10)70008-6  
13  
14 7  
15 8 15. Flórez García, MT. I Interventions to improve motor function in stroke patients. *Rehabilitación.*  
16 9 2000; 34(6): 423-37.  
17  
18 9  
19 10 16. Aziz NA, Leonardi-Bee J, Phillips M, Gladman JRF, Legg L, Walker MF. Therapy-based  
20 11 rehabilitation services for patients living at home more than one year after stroke. *Cochrane*  
21 12 *Database Syst Rev.* 2008; 2: CD005952. Doi: 10.1002/14651858.CD005952.pub2  
22  
23 12  
24 13 17. Langhorne P, Baylan S. Early supported discharge services for people with acute stroke.  
25 14 *Cochrane Database Syst Rev.* 2017; 7(7): CD000443. Doi: 10.1002/14651858.CD000443.pub4  
26  
27 14  
28 15 18. Roderick P, Low J, Peasgood T, Mullee MA, Turbull JC, Villar T et al. Stroke rehabilitation  
29 16 after hospital discharge: A randomized trial comparing domiciliary and day-hospital care. *Age*  
30 17 *Ageing.* 2001; 30(4): 303-10. Doi: 10.1093/ageing/30.4.303  
31  
32 17  
33 18 19. Coupar F, Pollock A, Legg LA, Sackley C, van Vliet P. Home-based therapy programmes for  
34 19 upper limb functional recovery following stroke. *Cochrane Database Syst Rev.* 2012; 5:  
35 20 CD006755. Doi: 10.1002/14651858.CD006755.pub2  
36  
37 20  
38 21 20. Outpatient Service Trialists. Therapy-based rehabilitation services for stroke patients at home.  
39 22 *Cochrane Database Syst Rev.* 2003; 1: CD002925. Doi: 10.1002/14651858.CD002925  
40  
41 22  
42 23 21. Minelli C, Gondim F, Antunes Barreira A, Dromerick A. Rehabilitation of the upper extremity  
43 24 and basic activities of daily living in the first month after ischemic stroke: an international  
44 25 cohort comparison study. *Neurol Int.* 2009; 1(1):e4. Doi: 10.4081/ni.2009.e4 22.  
45  
46 25  
47 26 22. Gilbertson L, Langhorne P, Walker A, Murray GD. Domiciliary occupational therapy for  
48 27 patients with stroke discharged from hospital: Randomised controlled trial. *BMJ.* 2000;  
49 28 320(7235): 603-6. Doi: 10.1136/bmj.320.7235.603  
50  
51 28  
52 29 23. Chaiyawat P, Kulkantrakorn K, Sritipsukho P. Effectiveness of home rehabilitation for  
53 30 ischemic stroke. *Neurol Int.* 2009; 1(1): 36-40. Doi: 10.4081/ni.2009.e10  
54  
55 30  
56 31 24. Björkdahl A, Nilsson ÅL, Grimby G, Sunnerhagen KS. Does a short period of rehabilitation in  
57 32 the home setting facilitate functioning after stroke? A randomized controlled trial. *Clin Rehabil.*  
58 33 2006; 20(12): 1038-49. Doi: 10.1177/0269215506071230  
59  
60



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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.
26. 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.
27. Paik YR, Kim SK, Lee JS et al. Simple and task-oriented Mirror Therapy for upper extremity function in stroke patients: A pilot study. *Hong Kong J Occup Th*. 2014; 24(1): 6-12. Doi: 10.1016/j.hkjot.2014.01.002
28. Toh SFM, Fong KNK. Systematic review on the effectiveness of mirror therapy in training upper limb hemiparesis after stroke. *Hong Kong J Occup Th*. 2012; 22(1): 84-95. Doi: 10.1016/j.hkjot.2012.12.009
29. Novaes MM, Palhano-Fontes F, Peres A Peres A, Mazzetto-Betti K, Pelicioni M, Andrade KC, et al. Neurofunctional changes after a single mirror therapy intervention in chronic ischemic stroke. *Int J Neurosci*. 2018; 128(10): 966-74. Doi: 10.1080 / 00207454.2018.1447571.
30. Fukumura K, Sugawara K, Tanabe S et al. Influence of mirror therapy on human motor cortex. *Int J Neurosci*. 2007; 117(7): 1039-48. Doi: DOI: 10.1080/00207450600936841
31. 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.
32. Zeng W, Guo Y, Wu G, Liu X, Fang Q. Mirror therapy for motor function of the upper extremity in patients with stroke: A meta-analysis. *J Rehabil Med*. 2018; 50(1): 8-15. Doi: 10.2340 / 16501977-2287.
33. Park JY, Chang M, Kim KM, Kim HJ. The effect of mirror therapy on upper-extremity function and activities of daily living in stroke patients. *J Phys Ther Sci*. 2015; 27(6): 1681-3. Doi: 10.1589/jpts.27.1681
34. Da Silva Costa V, Cunha da Silveira JC, Albuquerque Clementino TC, Dantas-de-Macedo-Borges LR, Trotásio de Melo L. Effects of mirror therapy on the motor and functional recovery of post-stroke paretic upper limbs: A systematic review. *Fisioter Pesqui*. 2016;23(4):431-8. Doi: 10.1590/1809-2950/15809523042016

- 1  
2  
3  
4 1 35. Oliveira e Castro P, Ferreira Pereira da Silva Martins MM et al. Mirror therapy and self-care  
5 2 autonomy after stroke: an intervention program. *Revista de Enfermagem Referência*. 2018;  
6 3 4(17): 95-106. Doi: 10.12707/RIV17088  
7  
8  
9 4 36. Perfetti C, Ghedina R, Jiménez Hernández D. El ejercicio terapéutico cognoscitivo para la  
10 5 reeducación motora del hemipléjico adulto. Barcelona: Edika Med; 1999. .  
11  
12 6 37. Domínguez Ferraz D, Da Silva-Ribeiro NM, De Matos-Pinheiro I, Pedreira Da Fonseca E.  
13 7 Eficacia del método Perfetti en el tratamiento de secuelas del accidente cerebrovascular: una  
14 8 revisión sistemática. *Cuest. fisioter*. 2014; 43(3): 196-205.  
15  
16 9 38. Díaz Castro WM, Rodríguez López YC. Método Perfetti como estrategia terapéutica en la  
17 10 rehabilitación de pacientes con enfermedad cerebrovascular: Revisión bibliográfica. *Mov*  
18 11 *Científico*. 2019; 13(1): 65-70. Doi: 10.33881/2011-7191.mct.13107  
19  
20 12 39. Sallés L, Martín-Casas P, Gironès X, Durà MJ, Lafuente JV, Perfetti C. A neurocognitive  
21 13 approach for recovering upper extremity movement following subacute stroke: A randomized  
22 14 controlled pilot study. *J Phys Ther Sci*. 2017; 29(4): 665-72. Doi: 10.1589 / jpts.29.665  
23  
24 15 40. Lee S, Bae S, Jeon D et al. The effects of cognitive exercise therapy on chronic stroke patients'  
25 16 upper limb functions, activities of daily living and quality of life. *J Phys Ther Sci*. 2015; 27(9):  
26 17 2787-91. Doi: 10.1589 / jpts.27.2787.  
27  
28 18 41. Cano de la Cuerda R, Molero Sánchez A, Carratalá Tejada M Alguacil-Diego IM, Molina-  
29 19 Rueda F, Miangolarra-Page JC, et al. Theories and control models and motor learning: clinical  
30 20 applications in neuro-rehabilitation. *Rev Neurol*. 2015; 30(1): 32-41. Doi: 10.1016 /  
31 21 j.nrl.2011.12.010.  
32  
33 22 42. Preissner K. Use of the occupational therapy task-oriented approach to optimize the motor  
34 23 performance of a client with cognitive limitations. *Am J Occup Ther*. 2010; 64(5): 727-34. Doi:  
35 24 10.5014/ajot.2010.08026  
36  
37 25 43. Khandare SS, Singaravelan RM, Khatri SM. Comparison of task specific exercises and mirror  
38 26 therapy to improve upper limb function in subacute stroke patients. *J Med Dent Sci*. 2013; 7(1):  
39 27 5-14.  
40  
41 28 44. Almhdawi KA, Mathiowetz VG, White M, del Mas RC. Efficacy of occupational therapy task-  
42 29 oriented approach in upper extremity post-stroke rehabilitation. *Occup Ther Int*. 2016; 23(4):  
43 30 444-56. Doi: 10.1002 / oti.1447.  
44  
45 31 45. Bayón-Calatayud M, Gil-Agudo A, Benavente-Valdepeñas AM Drozdowskyj-Palacios O,  
46 32 Sanchez-Martín G, Del Alamo-Rodríguez MJ. Efficacy of new therapies for upper limb  
47 33 neurorehabilitation in stroke patients. *Rehabilitación*. 2014; 48(4): 232-40.  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

46. Michaelsen SM, Dannenbaum R, Levin MF. Task-specific training with trunk restraint on arm recovery in stroke: Randomized control trial. *Stroke*. 2006; 37(1): 186-92. Doi: 10.1161/01.STR.0000196940.20446.c9
47. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J et al. Interventions for improving upper limb function after stroke. *Cochrane Database Syst Rev*. 2014; 11: CD010820. DOI: 10.1002/14651858.CD010820.pub2.
48. Vandana, Pattnaik M, Mohanty P. Effectiveness of mirror therapy in rehabilitation of hand function in sub-acute stroke. *Palliat Med Care*. 2017; 4(2): 1-9. Doi: 10.15226/2374-8362/4/2/00135
49. Ojeda-del-Pozo N, del-Pino-Sáez R, Ibarretxe-Bilbao N, Schretlen D, Peña J. Test Montreal Cognitive Assessment Test: normalization and standardization for Spanish population. *Rev Neurol*. 2016; 63(11): 488-96. Doi: 10.33588/rn.6311.2016241
50. French B, Thomas LH, Coupe J, McMahon E, Connell L, Harrison J et al. Repetitive task training for improving functional ability after stroke. *Cochrane Database Syst Rev*. 2016; 11(11): CD006073. Doi: 10.1002/14651858.CD006073.pub3
51. Pollock A, Baer G, Campbell P, Choo PL, Forster A, Morris J et al. Physical rehabilitation approaches for the recovery of function and mobility following stroke. *Cochrane Database Syst Rev*. 2014; 4(4): CD 091920 Doi: 10.1002/14651858.CD001920.pub3
52. Arya KN, Pandian S, Kumar D, Puri V. Task-Based Mirror therapy augmenting motor recovery in poststroke hemiparesis: A randomized controlled trial. *J Stroke Cerebrovasc Dis*. 2015; 24(8): 1738-48. Doi: 10.1016/j.jstrokecerebrovasdis.2015.03.026
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
54. Traversa R, Ccicinelli P, Oliveri M. Neurophysiological follow-up of motor cortical output in stroke patients. *Clin Neurophysiol*. 2000; 9(1): 1695-1703. Doi: 10.1016/S1388-2457(00)00373-4
55. Ferrer González BM. Adaptación y validación al español de la escala Fugl-Meyer en el manejo de la rehabilitación de pacientes con ictus [Doctoral thesis]. Universidad de Sevilla: 2016.
56. Doussoulin-Sanhueza A, Rivas-Sanhueza R. Validation and use Motor Activity Log and Action Research Arm scales as tools to assess the function of the paretic upper limb after a stroke in clinic and research. *Rev Mex Neurocienc*. 2014; 15(2): 138-46.

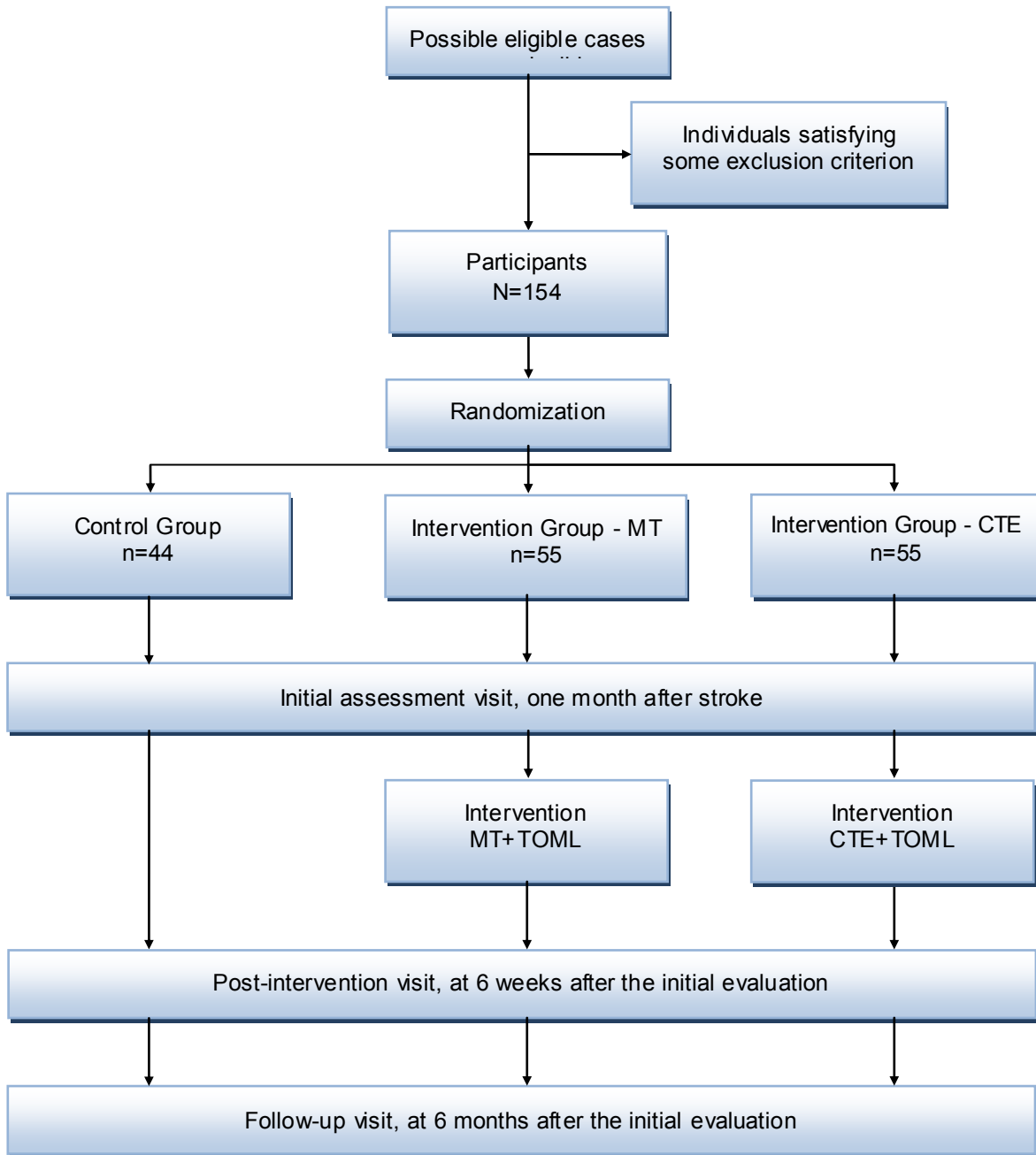
- 1  
2  
3  
4 1 57. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and Block Test of  
5 2 manual dexterity. *Am J Occup Ther.* 1985; 39(6): 386-91. Doi: 10.5014/ajot.39.6.386  
6  
7 3 58. Gómez-Soriano J, Cano-de-la-Cuerda R, Muñoz-Hellín E, Ortiz-Gutierrez R, Taylor JS.  
8 Evaluation and quantification of spasticity: a review of the clinical, biomechanical and  
9 4 neurophysiological methods. *Rev Neurol.* 2012; 55(4): 217-26. Doi: 10.33588/rn.5504.2012229  
10 5  
11 6 59. Fernández-Concepción O, Román-Pastoriza Y, Álvarez González MA, Verdecia-Fraga R,  
12 7 Ramírez-Perez E, Martínez-Gonzalez-Quevedo J et al. The development of a scale to evaluate  
13 the quality of life in stroke survivors. *Rev Neurol.* 2004; 39(10); 915-23. Doi:  
14 8 10.33588/rn.3910.2004133  
15 9  
16 10 60. Domínguez-Morales MR, Balmaseda-Serrano R, León-Carrión J, García-bernal M. Functional  
17 11 recovery of cerebrovascular patients after intensive treatment: preliminary data. *Revista*  
18 12 *Española de Neuropsicología.* 2012; 2(3): 44-61.  
19 13  
20 14 61. Jiménez-Caballero P, López-Espuela F, Portilla-Cuenca J, Pedrera-Zamorano D, Jiménez-  
21 15 Gracia MA, Lavado-García JM et al. Evaluation of the instrumental activities of daily living  
22 16 following a stroke by means of the Lawton and Brody scale. *Rev Neurol.* 2012; 55(6): 337-42.  
23 17 Doi: 10.33588/rn.5506.2012307  
24 18  
25 19 62. Montaner J, Alvarez-Sabin J. NIH stroke scale and its adaptation to Spanish. *Neurologia.* 2006;  
26 20 21(4): 192-202.  
27 21  
28 22 63. Arya KN, Verma R, Garg RK, Sharma VP, Aggarwal M, Aggarwal GG. Meaningful task-  
29 23 specific training (MTST) for stroke rehabilitation: A randomized controlled trial. *Top Stroke*  
30 24 *Rehabil.* 2012; 19(3): 193-211. Doi: 10.1310/tsr1903-193  
31 25  
32 26 64. Lisalde Rodríguez ME, García Fernández JA. Mirror therapy in hemiplegic patient. *Rev*  
33 27 *Neurol.* 2016; 62(1): 28-36. Doi: 10.33588/rn.6201.2015285  
34 28  
35 29  
36 30  
37 31  
38 32  
39 33  
40 34  
41 35  
42 36  
43 37  
44 38  
45 39  
46 40  
47 41  
48 42  
49 43  
50 44  
51 45  
52 46  
53 47  
54 48  
55 49  
56 50  
57 51  
58 52  
59 53  
60 54

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Figure 1: In the intervention set up for mirror therapy, the participant looks at the reflection of the unaffected hand in the mirror as if it was the affected hand.

277x270mm (96 x 96 DPI)





SPIRIT 2013 Checklist: Recommended items to address in a clinical trial- protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym - <i>Pag 1</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry - <i>Pag 11</i>
	2b	All items from the World Health Organization Trial Registration Data Set - - <i>Pag 11</i>
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support - <i>Pag 13</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors - <i>Pag 1</i>
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
<b>Introduction</b>		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention - <i>Pag 3-5</i>
	6b	Explanation for choice of comparators - <i>Pag 3-5</i>
Objectives	7	Specific objectives or hypotheses - <i>Pag 5</i>

1  
2 Trial design 8 Description of trial design including type of trial (eg, parallel group,  
3 crossover, factorial, single group), allocation ratio, and framework (eg,  
4 superiority, equivalence, noninferiority, exploratory) - *Pag 6*  
5  
6  
7

8 **Methods: Participants, interventions, and outcomes**  
9

10 Study setting 9 Description of study settings (eg, community clinic, academic hospital)  
11 and list of countries where data will be collected. Reference to where  
12 list of study sites can be obtained - *Pag 6*  
13

14 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility  
15 criteria for study centres and individuals who will perform the  
16 interventions (eg, surgeons, psychotherapists) - *Pag 6*  
17  
18

19 Interventions 11a Interventions for each group with sufficient detail to allow replication,  
20 including how and when they will be administered - *Pag 7-8*  
21

22 11b Criteria for discontinuing or modifying allocated interventions for a  
23 given trial participant (eg, drug dose change in response to harms,  
24 participant request, or improving/worsening disease)  
25

26 11c Strategies to improve adherence to intervention protocols, and any  
27 procedures for monitoring adherence (eg, drug tablet return,  
28 laboratory tests)  
29

30 11d Relevant concomitant care and interventions that are permitted or  
31 prohibited during the trial  
32  
33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific  
35 measurement variable (eg, systolic blood pressure), analysis metric  
36 (eg, change from baseline, final value, time to event), method of  
37 aggregation (eg, median, proportion), and time point for each  
38 outcome. Explanation of the clinical relevance of chosen efficacy and  
39 harm outcomes is strongly recommended - *Pag 9-10*  
40  
41

42 Participant 13 Time schedule of enrolment, interventions (including any run-ins and  
43 washouts), assessments, and visits for participants. A schematic  
44 diagram is highly recommended (see Figure) - *Pag 8 - Pag 10*  
45

46 Sample size 14 Estimated number of participants needed to achieve study objectives  
47 and how it was determined, including clinical and statistical  
48 assumptions supporting any sample size calculations - *Pag 6*  
49  
50

51 Recruitment 15 Strategies for achieving adequate participant enrolment to reach  
52 target sample size - *Pag 6*  
53

54 **Methods: Assignment of interventions (for controlled trials)**  
55

56 Allocation:  
57  
58  
59  
60



1			
2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions - <i>Pag 7</i>
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned - <i>Pag 7</i>
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions - <i>Pag 7</i>
17			
18			
19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how - <i>Pag 10</i>
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial
26			
27			

### Methods: Data collection, management, and analysis

28			
29			
30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol
36			
37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol
46			
47			
48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods		Reference to where other details of the statistical analysis plan can be
50			found, if not in the protocol
51			
52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses)
54			
55		20c	Definition of analysis population relating to protocol non-adherence
56			(eg, as randomised analysis), and any statistical methods to handle
57			missing data (eg, multiple imputation)
58			
59			
60			

## Methods: Monitoring

- 1  
2  
3  
4 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role  
5 and reporting structure; statement of whether it is independent from  
6 the sponsor and competing interests; and reference to where further  
7 details about its charter can be found, if not in the protocol.  
8 Alternatively, an explanation of why a DMC is not needed - *Pag 10*  
9  
10  
11 21b Description of any interim analyses and stopping guidelines, including  
12 who will have access to these interim results and make the final  
13 decision to terminate the trial - *Pag 10*  
14  
15 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and  
16 spontaneously reported adverse events and other unintended effects  
17 of trial interventions or trial conduct - *Pag 10*  
18  
19 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and  
20 whether the process will be independent from investigators and the  
21 sponsor  
22  
23

## Ethics and dissemination

- 24  
25  
26 Research ethics 24 Plans for seeking research ethics committee/institutional review board  
27 approval (REC/IRB) approval - *Pag 11*  
28  
29 Protocol 25 Plans for communicating important protocol modifications (eg,  
30 amendments changes to eligibility criteria, outcomes, analyses) to relevant parties  
31 (eg, investigators, REC/IRBs, trial participants, trial registries, journals,  
32 regulators)  
33  
34  
35 Consent or assent 26a Who will obtain informed consent or assent from potential trial  
36 participants or authorised surrogates, and how (see Item 32)  
37  
38 26b Additional consent provisions for collection and use of participant data  
39 and biological specimens in ancillary studies, if applicable - *No*  
40 *applicable*  
41  
42  
43 Confidentiality 27 How personal information about potential and enrolled participants will  
44 be collected, shared, and maintained in order to protect confidentiality  
45 before, during, and after the trial - *Pag 10-11*  
46  
47  
48 Declaration of 28 Financial and other competing interests for principal investigators for  
49 interests the overall trial and each study site - *Pag 13*  
50  
51 Access to data 29 Statement of who will have access to the final trial dataset, and  
52 disclosure of contractual agreements that limit such access for  
53 investigators - *Pag 10*  
54  
55 Ancillary and 30 Provisions, if any, for ancillary and post-trial care, and for  
56 post-trial care compensation to those who suffer harm from trial participation  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15
- |                         |     |   |
|-------------------------|-----|---|
| Dissemination<br>policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions - <i>Pag 12</i> |
|                         | 31b | Authorship eligibility guidelines and any intended use of professional writers - <i>Pag 12</i>  |
|                         | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code - <i>Pag 12</i>   |

## 16 Appendices

- 17  
18  
19  
20  
21  
22  
23  
24
- |                               |    |  |
|-------------------------------|----|--|
| Informed consent<br>materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates - <i>Available</i>  |
| Biological<br>specimens       | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

---

25 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013  
26 Explanation & Elaboration for important clarification on the items. Amendments to the  
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT  
28 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)"  
29 license.  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60