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

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

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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 6th and 13th 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[1].

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

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[4–5,7]. 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[8].

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[9]. 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[3,9–12]. Most studies have demonstrated the importance of patient-centered interventions, as well as the need to

combine different techniques, thereby not centering the treatment on a single modality[10,13–14].

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

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

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

Factors such as age, cognitive capability, and finger-related motor functioning of the affected or dominant hand can influence the degree of effectiveness of MT in patients with hemiparesis[7]. Therefore, the majority of studies coincide over the need for further research in this area[16–24].

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

CTE has demonstrated its effectiveness in improving muscle strength, tactile sensorial discrimination and kinesthetics, the functionality of the upper hemiplegic or hemiparetic extremities, and the quality of life of stroke patients[26–29]. However, despite the fact that it is one of the most complete and effective methods for the rehabilitation of

neurological deficit in the upper extremities[26], new studies with homogeneous samples of greater size are warranted, which could define aspects such as the time and the materials necessary for their implementation[25–27].

TOML is an effective method to promote and stimulate motor skills and neuronal plasticity in patients with injuries to the Central Nervous System (CNS). It comprises screening of the patient to develop personal strategies for performing useful functional movements in different contexts and situations[29]. Training of the paretic hemibody is performed under suitable conditions through specific, repetitive, and intensive tasks, of significance to the patient[29–32]. By actively participating in the rehabilitation process, intervening in the search and the discovery of strategies, personal functional independence is improved and the adaptation of the patient to the environment is assisted[29]. This rehabilitation technique employs five strategies to teach and motivate the patient, who must adapt to the requirements of each task: verbal instructions, visual demonstrations, manual guide, reinforcement, and positive feedback, and its repetitive practice in different contexts[13].

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

In view of the above, a comparative study between MT and CTE has been planned. Even though these two techniques are effective in neuro-rehabilitation, their comparative effectiveness, or the answer to the question as to which one would yield better results, as well as their maintenance over time is yet to be confirmed. The objective of the present study is, therefore, to analyze and compare the effectiveness of MT and CTE, in combination with TOML, in the optimization of the upper extremities of stroke patients with residual hemiparesis and their movement patterns, in such a manner so as to achieve maximum functionality of the upper extremity, correct the improper compensation strategies and achieve functionally useful movements.

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[37], with a score on the Montreal Cognitive Assessment (MoCA) scale[38] equal to or over 26. All participants will require to sign an informed consent form. Participants presenting hemineglígence, Wernicke's asphasia, 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 α 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.

It has been estimated that 55 participants would be required in each intervention group. An additional 44 individuals will be needed for the calculation of the size of the spontaneous improvement group, which is bound to occur in 20% of the cases as per the estimates[39].

Randomization

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

Intervention

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

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

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

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

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

Three different modalities will be used in accordance with the function of the pathological element to be recovered. With the first modality (first degree), an attempt will be made to control the exaggerated resistance of muscle tonicity to passive stretching and to surmount the deficits of tactile and kinesthetic sensitivity rather than the patient activating a particular motor unit, the therapist will manipulate the whole movement. Throughout the second modality (second degree), an attempt will be made to control the involuntary activation of muscle groups, not directly involved with the action that has been performed, including inferences of weight, grip, and friction, with minimum assistance from the therapist. It will be introduced in combination with the movements from the first-degree modality, when the patient will have acquired a certain degree of control over the recruitment of motor units. In the third-degree modality, the control of voluntary movements and decisions on their fragmentation, variability, and adaptation, with the objective of perfect automatization of the movement, all without the therapist will be emphasized; it is anticipated that all the exaggerated responses should have been achieved in the earlier exercises. The sessions will commence with exercises from the first-degree modality, progressively increasing the degree of difficulty, in accordance with the improvements observed and the needs of the patient. All the exercises used in one modality can be adapted to another.

Procedure

An initial evaluation visit will be programmed for the 4th week after stroke and two follow-up visits in the 6^{th} and 13^{th} weeks after the initial visit, in which an assessment of their state will be completed with the help of different instruments and questionnaires. All participants included in the IG will receive 30 treatment sessions, distributed between the initial evaluation and the first follow-up visit (Figure 1).

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[40], which assesses motor functioning, passive articular mobility, articular pain, coordination, and balance.
- The Action Research Arm Test (ARAT)[41], which measures the functionality of the upper limb.
- The Motor Activity Log (MAL–30)[41], 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)[42], which assesses the manipulative value of the hand.
- The Ashworth Scale[43], which measures the spasticity of the upper limb.

Cognitive performance

The cognitive performance will be evaluated by the MoCA scale[38], 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][44], 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[45]. The 30 items in this instrument are used to assess the

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

The instrumental activities of daily living (IADL) will be evaluated using the Lawton-Brody index[46]. It assesses the capability to develop tasks involving the handling of every-day utensils and day-to-day social activities, including the use of telephone, shopping, preparing meals, household work, washing clothes, use of transport, responsibility with respect to medication, and the management of economic affairs.

Other measures/co-variables

The following variables will be evaluated to control for possible predictive or confusion factors: age, sex, type of stroke, affected cerebral hemisphere and stroke severity as quantified by the National Institute Health Stroke Scale (NIHSS)[47].

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

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

Blinding strategy

This is not a blind study, owing to the nature of the intervention, the participants, and the fact that the researcher is responsible for conducting the therapy. However, strategies will be implemented to ensure that it is as blind a study as possible. Different researchers will be employed for carrying out the assessment visits and conduction of the therapy, regardless of the group to which the participants belong. In addition, clear instructions will be given to the participants, not to reveal the group to which they have been assigned during the assessment visits. The researcher responsible for statistical analysis will be blinded to the participant's group.

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 α 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[16–23]. The review completed by Lisalde-Rodríguez[48] 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[31]. The study by Kyunghoon et al.[9] 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[26].

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

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

This work will provide novel and useful data for the development of post-stroke rehabilitation strategies. The intervention may provide implications for the preparation of evidence-based recommendations, practical clinical guides, and continuous quality improvement programs that target post-stroke patients.

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

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Legends of figures:

- **Figure 1**: Study flow chart.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym - *Pag 1*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry - *Pag 11*
	2b	All items from the World Health Organization Trial Registration Data Set - - *Pag 11*
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support - *Pag 13*
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors - *Pag 1*
	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)
Introduction		
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 - *Pag 3-5*
	6b	Explanation for choice of comparators - *Pag 3-5*
Objectives	7	Specific objectives or hypotheses - *Pag 5*

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

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained - *Pag 6*
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) - *Pag 6*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered - *Pag 7-8*
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended - *Pag 9-10*
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) - *Pag 8 - Pag 10*
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations - *Pag 6*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size - *Pag 6*

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions - *Pag 7*
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned - *Pag 7*
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions - *Pag 7*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how - *Pag 10*
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

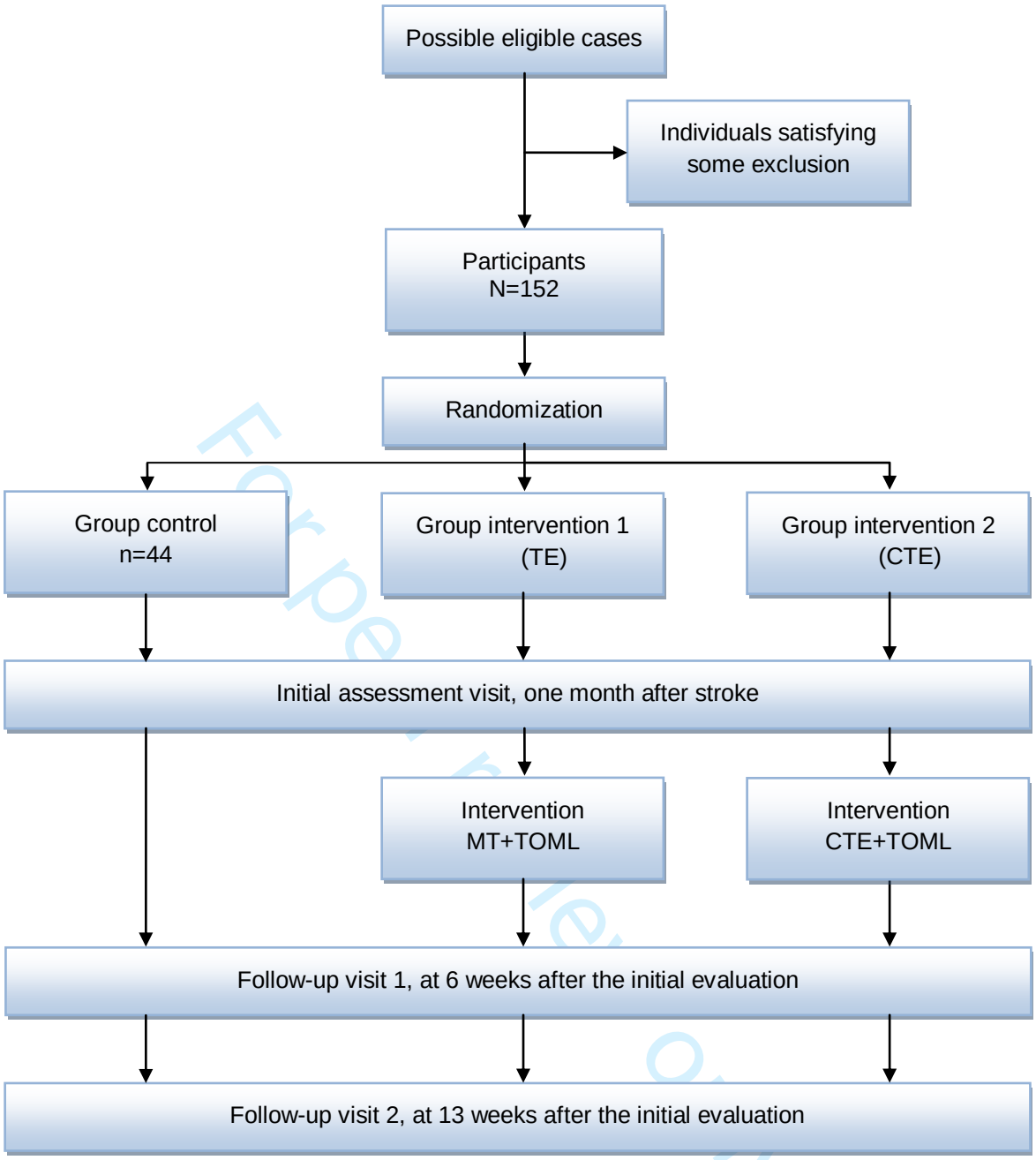
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively,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

Ethics and dissemination

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

Dissemination 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 - *Pag 12*
	31b	Authorship eligibility guidelines and any intended use of professional writers - *Pag 12*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code - *Pag 12*
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates - *Available*
Biological 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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.



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.

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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.

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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.

STRENGTHS AND LIMITATIONS OF THE STUDY

- This study will use stroke-related neurorehabilitation techniques, which would enable an easy at-home application to the patient.
- The sample size will provide greater confidence and credibility regarding the benefits of these neurorehabilitation approaches and help in understanding the relevant aspects to conduct future studies.
- Because of the nature of the intervention, the participants will not be blinded; however, the researchers who perform the measurements and statistical analysis will be blinded.

INTRODUCTION

The World Health Organization 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 more than 24 hs[1].

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

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

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

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

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

Mirror Therapy

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

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

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

Cognitive Therapeutic Exercise

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

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

CTE has been effective in improving muscle strength, tactile sensorial discrimination and kinesthetics, the functionality of the upper hemiplegic or hemiparetic extremities, and the quality of life of patients after stroke[38–41].

However, despite the fact that it is reported as one of the most complete and effective methods for the rehabilitation of neurological deficit in the upper extremities[38], new studies with a larger sample size are warranted, which could define aspects such as time and materials required for their implementation[37–39].

Task-oriented training

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

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

Thus, a comparative study between MT and CTE has been planned. Although moderate-quality evidence exists to suggest that both techniques are effective in neurorehabilitation, their comparative effectiveness, or the one that yields better results and maintenance over time is yet to be confirmed[47]. Therefore, the objective of this study is to evaluate which of these techniques combined with task-oriented training is more effective in functional recovery and movement patterns of the upper extremities in patients with severe hemiparesis after stroke.

METHODS AND ANALYSIS

Design and setting

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

Study population

The participants will be recruited at the point of discharge from the Neurological Service and Stroke Unit of the Burgos University Hospital (Spain) by means of consecutive sampling. This is the only third-level health center for the referral of patients with stroke in the region. All evaluation and follow-up visits and the development of the interventions will be carried out in the patient's home.

All participants meeting the following inclusion criteria would be included in the study: patients of both sexes, those aged 18 years or above, those with a diagnosis of residual hemiparesis because of ischemic or hemorrhagic stroke, those whose movements of the affected upper extremities are

classified between stages II and IV on the Brunnstrom Scale[48], and those with a score on the Montreal Cognitive Assessment (MoCA) scale[49] equal to or above 26. All participants will be required to sign an informed consent form. Participants presenting hemineglglect, Wernicke's aphasia, mixed aphasia, and/or visual deficits (homonymous hemianopsia) will be excluded from the study, considering the diagnostic information provided by the clinical assessment of neurologist.

Patient and public involvement

The patients and the public will participate in the study design so that time and spaces necessary for the home-based intervention could be adapted according to their availability. Moreover, they will be part of the data collection process and will be informed of the results obtained. Participants may suggest changes related to the frequency and intensity of the sessions. The results will be disseminated through communications, including media, healthcare institutions, patients' associations for 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 has been estimated on the basis of the potential modification of the main variable, i.e., the functionality of the affected upper extremity. Given alpha and beta risks of 0.05 and 0.20, respectively, in bilateral contrast, 110 participants (55 per group) will be required to detect a minimum difference of 0.50 in the functionality of the affected upper extremity using the Fugl-Meyer Assessment (FMA) between the two groups. An additional 44 individuals will be needed for calculating the size of the spontaneous improvement group, which is estimated to occur in 20% of the cases[48]. A predicted dropout rate of 10% during follow-up has been considered.

Randomization

Participants will be randomly assigned either to a control group (CG) or an intervention group (IG). An assignation sequence in masking clusters at a ratio of 1:1:1 will be centrally generated by an independent researcher using the Epidat 4.2 program before the inclusion of the participants.

Intervention

The standard rehabilitation treatment for stroke will be used for all study participants. Participants included in the CG will not receive any additional treatment or therapy.

IG^{-1} will receive an additional treatment of MT with task-oriented training, whereas IG–2 will receive CTE with task-oriented training. In both groups, the interventions will begin at the participant's home during a period of six weeks (30 days), including 60-minute sessions, 30 min of which will be for MT or CTE, and the remaining 30 min will be for task-oriented training.

Task-oriented training

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

Mirror Therapy

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

MT can be used in three different modes. In the first mode, the patient tries to imitate the movement of the healthy hand with the affected hand in a synchronized way. In the second mode, the patient only imagines that the reflected movement of the healthy hand is being performed by his affected hand. In the third mode, the therapist assists patient's affected hand to imitate the movement performed by the healthy hand. Considering these modes, first simple exercises without objects were performed with the healthy hand while imagining the same movement with the affected hand; then, the same movements are performed by the affected hand with the help of the therapist[51,52].

Simple movements without any objects will be performed during the first 10 sessions, and then, simple movements using objects will be performed in the following 10 sessions. Moreover, movements of greater complexity with objects will be included in the last 10 sessions. To be more specific, the patient will complete movements with a healthy hand throughout the first three groups

of 10 sessions and will try to imagine them with the affected hand (mode). Those movements will be assisted by a therapist in the three subsequent sessions (mode), whereas the patient will try to imitate the movements of the healthy hand by the affected hand throughout the last four sessions (mode). All the exercises will have to be completed slowly and repeated at least 15 times. The activities and their levels of complexity will be adjusted as per the limitations and capabilities of each patient[51,52].

Cognitive Therapeutic Exercise

The cognitive therapeutic exercises (CTE) are classified according to multiple criteria in three different modalities: first, second, and third grades. All patients will begin performing the first-grade exercises until they regain the ability to control the reaction to stretching to graduate intensity, time, and spatiality. Once the patient can successfully perform the first-degree exercises, control the reactions to stretching in a sufficiently automated way, and frequently perform selective movements of the fingers and other body segments, the second-degree exercises are performed[39,53].

Finally, third-degree exercises are performed through which the patient learns to adapt movements to the proposed perceptual hypothesis after the patient has managed to automate the control of abnormal motor behaviors with the second-degree exercises. The criteria that must be considered to establish correct programming of the exercises depend on the configuration of the trajectories that are requested from the patient and on the intensity of the contractions that must be activated in the segments that execute them[36].

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

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

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

Procedure

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

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

Primary and secondary endpoints

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

The functionality of the affected upper extremity

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

- The FMA[55], which assesses motor functioning, passive articular mobility, articular pain, coordination, and balance;

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

Cognitive performance

The cognitive performance will be evaluated using the MoCA scale[49], distributed into seven different cognitive domains: visuospatial 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 (Scale of PostStroke Quality of Life)[59], which comprises 38 items grouped into eight domains: physical state, communication, cognition, emotions, feelings, BADL, common ADL, and socio-family functioning.

Performance of ADL

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

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

Other measures/covariables

The following variables will be evaluated to control the possible predictive or confusion factors: age, sex, type of stroke, affected cerebral hemisphere, and stroke severity, quantified by the National Institute Health Stroke Scale[62].

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 χ^2 test or Fisher's exact test. The means between the two groups will be compared using the Student's t-test or the Mann-Whitney U-test. Pearson's or Spearman's correlation coefficients will be calculated to analyze the relationship between quantitative variables. A p-value of <0.05 was considered statistically significant. The statistical

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

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

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

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

Analysis by subgroups

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

Secondary analysis

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

ETHICS AND DISSEMINATION

Ethical considerations

The study has been approved by the Clinical Research Ethics Committee 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 identifier no. NCT04163666.

In accordance with the Helsinki Declaration, prior informed consent will be obtained from the individuals who voluntarily decide to participate. They will be informed of the objectives, risks, and benefits of the assessments, as well as the interventions that will be used. None of the activities 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 be as per the recommendations mentioned in the CONSORT declaration. This study will be 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 primary outcome (functionality of the upper extremity) and the other on the secondary results. The results will be disseminated through communications, including media and social networks, as well as at international and national scientific conferences and seminars. Similarly, a doctoral thesis based on the content of this project will be developed.

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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Competing interests: None declared

Legends of figures:

1. **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.
2. **Figure 2**: Study flow chart.

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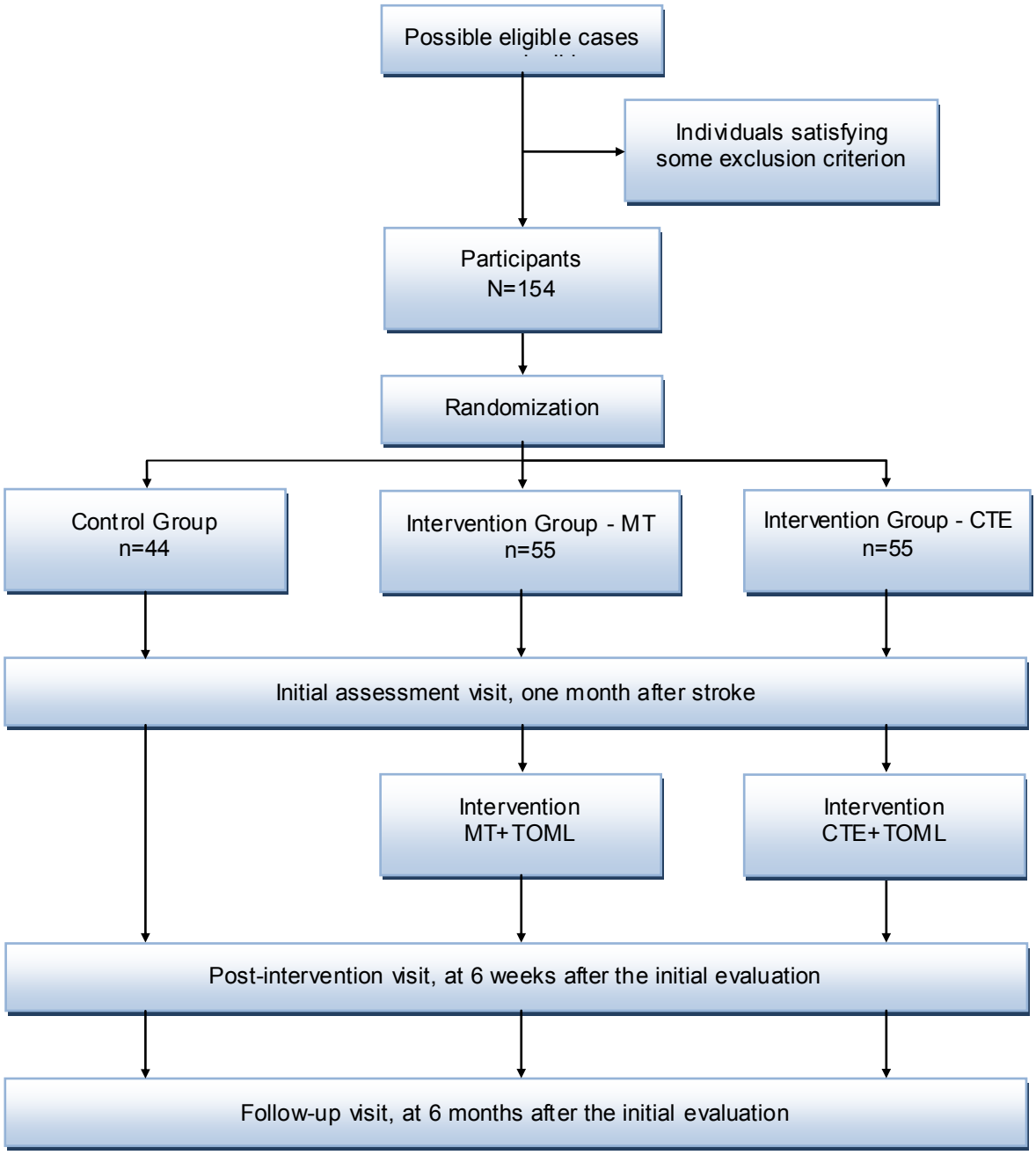
Figure 1: In the intervention set up for mirror therapy, the participant looks at the reflection of the unaffected hand in the mirror as if it was the affected hand.

277x270mm (96 x 96 DPI)


Possible eligible cases
Individuals satisfying some exclusion criterion
Participants N=154
Randomization
Control Group n=44
Intervention Group - MT n=55
Intervention Group - CTE n=55
Initial assessment visit, one month after stroke
Intervention MT+TOML
Intervention CTE+TOML
Post-intervention visit, at 6 weeks after the initial evaluation
Follow-up visit, at 6 months after the initial evaluation

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym - *Pag 1*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry - *Pag 11*
	2b	All items from the World Health Organization Trial Registration Data Set - - *Pag 11*
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support - *Pag 13*
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors - *Pag 1*
	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)
Introduction		
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 - *Pag 3-5*
	6b	Explanation for choice of comparators - *Pag 3-5*
Objectives	7	Specific objectives or hypotheses - *Pag 5*

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

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained - *Pag 6*
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) - *Pag 6*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered - *Pag 7-8*
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended - *Pag 9-10*
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) - *Pag 8 - Pag 10*
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations - *Pag 6*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size - *Pag 6*

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions - *Pag 7*
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned - *Pag 7*
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions - *Pag 7*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how - *Pag 10*
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

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

Ethics and dissemination

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

Dissemination 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 - *Pag 12*
	31b	Authorship eligibility guidelines and any intended use of professional writers - *Pag 12*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code - *Pag 12*
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates - *Available*
Biological 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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.