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A Calligraphy-based Rehabilitation Exercise for Improving the Upper-limb Function of Stroke Patients: Protocol for A Randomized Controlled Study

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Abstract

Introduction: A common complication of stroke is upper-limb dysfunction. Chinese calligraphy handwriting (CCH) is an aesthetical exercise developed from the traditional way of writing in China and holds potential to become a rehabilitation method to improve the upper-limb function of stroke patients. This study aims to design a randomized controlled trial to assess the effect of a customized CCH-based exercise for post-stroke rehabilitation of upper-limb dysfunction.

Methods and analysis: A single-blinded randomized controlled trial will be conducted on 60 stroke patients. The patients will be randomly allocated into three groups: 1) conventional occupational therapy (COT) group; 2) COT+CCH group; 3) COT+ Graded Repetitive Arm Supplementary Program (GRASP) group. For the COT group, patients will receive COT treatment 1 hour per day. For the COT+CCH group, patients will receive 30-mins COT treatment and 30-mins CCH training. For the COT+GRASP group, patients will receive 30-mins COT treatment and 30-mins GRASP training. All the interventions will be performed 5 days per week for a total of 3 weeks. The upper-limb functions will be assessed before and after the interventions using a series of rating scales.

Ethics and dissemination: This study has been approved by the Research Ethics Committees of the Second Rehabilitation Hospital of Shanghai (Study ID: 2020-32-01) and the Shanghai University of Sport (Study ID: 102772021RT043). Results will be directly disseminated to the patients at the end of the study, and to the publics via publications in peer-reviewed journals and presentations in conferences.

Trial registration number: Chinese Clinical Trials Registry (ChiCTR 2100043036)

Keywords: Rehabilitation; Stroke; Calligraphy; Upper limb function; Protocol; Motor control

Article summary

Strengths and limitations of this study

- This study will be the first randomized controlled trial to explore the effects of Chinese calligraphy handwriting in regard to facilitating hemiparetic upper limb recovery in patients with stroke.
- The Chinese Calligraphy is a culture-based self-performed exercise with minimized risk so that patients can continue to perform this exercise after returning home from the hospital.
- This study is single-blind study. Patients and therapist delivering the intervention cannot be blinded to the intervention allocation, which potentially introduces a source of bias.

Introduction

Recent epidemiological studies reveal that near 17 million people suffer from stroke per year in the world [1-3], and only in China over 2.5 million new stroke cases are diagnosed per year [3, 4]. With the improved care in the hyperacute and acute periods of stroke, around 80% of the stroke patients can survive from the initial injuries [5]. However, the stroke can usually lead to severe complications in the patients, such as neuropsychiatric disorders and impairments on motion capacities, sensory, and cognitive [6, 7]. As one of the most common complications, the motor impairment may affect the unilateral movement abilities of patients' upper limbs [8, 9]. The patients with such upper-limb dysfunctions would exhibit difficulties in contracting the muscles, as well as controlling and coordinating their arms, hands, and fingers. The post-stroke upper-limb dysfunctions can thus limit the patients in their abilities in daily lift such as eating, dressing and washing [10-12], and increase their dependences and affect the quality of life in long term [13]. Therefore, post-stroke rehabilitation of upper-limb dysfunction is critical to restoring patients' upper-limb functions and improving their living abilities [14].

By leveraging different technologies, multiple post-stroke rehabilitation therapies have been developed and used to restore upper-limb functions, such as therapist-assisted practice [15-17], bilateral training [18], constraint-induced movement therapy (CIMT) [19], robotic-assisted therapy [20], mirror therapy [21], and virtual reality [22]. As the function recovery can last into the chronic phase of stroke [23], there is increasing interest in validating interventions that aim at enhancing physical and psychological well-beings in both acute and chronic periods of post-stroke rehabilitation. It is becoming wide-accepted that the therapies involving high-intensity repetitive tasks, such as the CIMT, have the best effect on recovering the upper-limb functions [8]. However, the CIMT forces the patient to use the impaired arm by limiting the contralateral arm, and thus challenges the patient's compliance during practicing [19, 24] and affects the treatment outcomes [25, 26]. Therefore, the high-intensity repetitive therapies may not be optimal for long-term rehabilitation of post-stroke upper-limb dysfunctions as well as improving psychological well-beings of the patients. The therapies supervised by therapists or with sophisticated equipment can increase the financial pressure of the patients [27, 28], and thus may not be wide accepted for long-term persistence. Therefore, economical and easy-to-adherence interventive exercises should be developed and involved into

current post-stroke rehabilitation programs, in order to allow the patients to persist the training to obtain ongoing benefits from the therapy.

Chinese calligraphy handwriting (CCH) is a culture-based exercise to express the aesthetics of Chinese characters and writer's inner psyche [29]. Clinically, the CCH process has been found to be able to facilitate people's psychosomatic and cognitive wellbeing [30], and exerts curative effects on autism, depression, and posttraumatic stress disorder [29]. For example, it was reported that CCH could improve specific cognitive functions of the patients with mild cognitive impairment [31]. It was also reported that CCH could normalize physiological arousal parameters of cancer survivors, including slower heart rate, decreased blood pressure, and decelerated respiration [32]. Thus, the CCH may be able to mitigate the post-stroke neuropsychiatric disorders. More importantly, the CCH may be a proper exercise to improve the stroke patients' upper limbs functions because of its unique writing styles. Firstly, the writer needs to maintain the upper-limb stability to smooth the thickness of character strokes during the CCH, which makes it an effect way to stimulate muscle contractions of the upper limb. Secondly, the writer strives to control the writing speed and frequently alter the tilt angles during writing. Performing the CCH thus may be able to train the coordinative movements and improve the flexibility of upper-limb joints. Finally, the writer needs to imagine the configurations of the characters (e.g. position, size), and perform writing while simultaneously recalling and retrieving the configurations, which may be able to improve the patient's cognitive well-being, hand-eye coordination, and real-time execution ability [33]. Therefore, the CCH holds great potentials in facilitating the recovery of upper-limb functions as well as improving the mental state of stroke patients.

The cultural factors behind the CCH may make it more easily accepted by Chinese patients than many other exercises. Calligraphy copybook is prevalently used at the beginning of CCH self-practicing because the character frames in the copybook can regulate people's writing styles without the need of instructors. The calligraphy copybook thus is an excellent tool for the stroke patients to practice CCH exercise at both hospital and home. Therefore, the purpose of this study is to develop a CCH-based interventive exercise with self-designed calligraphy copybook and validate its effect on improving patients' upper-limb functions in the chronic period of stroke.

Methods

Study design

This study will be a single-center, three-arm, parallel group, assessors-blind randomized controlled trial. All the patients will be informed of the study content before the subject recruitment. The patients who meet the inclusion criteria and agree to participant the study will sign the informed consent. As shown in the study flow chart (Figure 1), the patients will be randomly allocated into 3 groups with equal simple size: 1) conventional occupational therapy (COT) group; 2) COT+CCH group; 3) COT+ Graded Repetitive Arm Supplementary Program (GRASP) group. The rehabilitation interventions will last 3 weeks. Patients' upper-limb functions will be assessed using rating scales before and after the interventions. The study protocol, including enrollment, intervention, and assessment, is shown in Figure 2 (recommended for interventional trials (SPIRIT) 2013) [34].

Subject recruitment and randomization

From January 2021 to September 2021, patients will be screened and recruited among the Department of Neurological Rehabilitation in the Second Rehabilitation Hospital of Shanghai via reviewing their electronic medical records. This study will only recruit patients who meet the following criteria: 1) first-ever stroke through neuroimaging assessment; 2) within the chronic phase of stroke; 3) able to sit without upper-limb supporting; 4) sufficient active range of motion: 90° of shoulder flexion, 90° of elbow flexion, 30° of wrist pronation/supination, 30° of wrist flexion; 5) able to hold the calligraphy brush with the affected hand; 6) good cognitive ability (Mini-Mental State Exam scores > 23) [35]; 7) no serious visual impairment or visual field defect; 8) 40-80 years old. Patients won't be recruited if they have: 1) other neurological diseases or upper-limb surgical histories; 2) severe communication deficits; 3) obvious shoulder pain (pain rating at rest > 5) [36].

Subject randomization will be performed by an external professional statistician. Number 1-60 will be randomly sequenced using the SPSS V.23.0. 60 envelopes will be prepared, each with an external series number corresponding to the random sequence generated and an internal group number: #1 (COT group), #2 (COT+CCH group), or #3 (COT+GRASP group) [37]. Once a patient is recruited, the authors will open an envelope sequentially and allocate the patient into a group according to the internal group number. The

external series number on the envelop will also be used as the ID of each patient for tracking their information and data throughout the entire study, which can make the assessor blind to the group allocation.

Sample size

According to a previous study [38], the effect size of detecting a minimally clinically important difference in the Action Research Arm Test scale in the patients with acute stroke is 1.10. The sample size was then calculated using this value in G*Power 3 (Erdfelder, Faul, & Buchner, 1996). To achieve a power of 80% ($\alpha = 0.05$), a minimum of 15 subjects is required for each group. Taking this rate into consideration, a final estimation of 60 patients (20 per group) is needed in the study.

Interventions

All the patients will receive rehabilitation interventions on the basis of routine treatment and daily nursing in the hospital. The rehabilitation interventions will be carried out 5 days per week for a total of 3 weeks. The patients will be allowed to consult with the research team at any time during the interventions. If any patient reports severe complications that may affect the ongoing of the interventions, her/his test will be terminated with corresponding reasons being recorded, and routine rehabilitation treatment will be provided.

In the COT group, the patients will receive 60-mins COT treatment every day. The t treatment will be performed by a therapist, which comprises task-related practices for gross movements and dexterity, including different grips, selective finger movements, strength training, stretching, and daily life activities.

In the COT+CCH group, the patients will receive 30-mins COT treatment and 30-mins CCH training every day. The CCH training will be performed on self-designed copybooks with hollowed-out character frames (Figure 3a). The copybooks are reusable because the water can dry out in 5 minutes. During writing, the patients will be required to sit steadily in front of a desk. The patients hold a calligraphy brush using the thumb, index finger, and middle finger of their affected hands, soak its head with water, and then fill the character frames on the copybook (Figure 3b). 3 different copybooks with increasing difficulties are designed, and each will be used in the CCH training for 1 week (Figure 3c). This design can enable the patients imitating geometric shapes beginning with straight lines, followed by more complicated circles and curves, which will comply the skill relearning progression within the post-stroke rehabilitation [39].

In the COT+GRASP group, the patients will receive 30-mins COT treatment and 30-mins GRASP training every day. The GRASP is a standardized post-stroke upper-limb rehabilitation program [40], and has been demonstrated effective in enhancing the motor function of the upper limb of chronic stroke patients [41]. with an exercise manual presenting the schematic diagrams of each exercise as well as exercise equipment. During the GRASP training, the therapist will leverage simple tools (such as balls, cups, and towel) to guide the patients to practice the actions and skills involved in daily activities [42].

Outcome assessment

The effects of these interventions on patients' upper-limb functions and quality of life will be assessed using a couple of different rating scales by a senior physiotherapist with over 5-years relevant experiences. The rating scales include:

1) Primary outcome measures

- Action Research Arm Test (ARAT) [43]: The measure is a 19-items test divided into 4 subtests (grasp, grip, pinch and gross movement). For each item, the patient is asked to perform a simple task that involves a functional movement of the affected upper limb.

2) Secondary outcome measures

- Fugl-Meyer assessment-UE (FMA-UE) [44]: This measure is designed to assess motor function, sensation, balance, range of motion, and joint pain.
- Griping strength of the affected hand will be measured as the mean of 3 consecutive trials.
- Purdue pegboard (PPB) [45]: The is a reliable measure to assess the gross movement of the arm, hand and fingers, as well as the fingertip dexterity. This measure requires patients to pick up pins one at a time and place them in a row of hole.
- Disabilities of arm, shoulder, and hand (DASH) [46]: This measure is a 30-item self-report questionnaire, which is designed to assess individually rated upper limb impairments and impacts on activities for patients with musculoskeletal conditions in the upper limbs.
- Quality of life (short form 36, SF-36) [47]: This measure is a generic self-report of health status for evaluating quality of life that relates to physical and mental well-beings.

Statistical method

Two-way analysis of variance (ANOVA) will be applied to examine the interaction and the main effects of the intervention method and the assessment time. 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. If significant difference is found, post hoc analysis will be carried out using Tukey's test. Demographic characteristics and other baseline values will be described using descriptive statistics for each group. Significant level will be set at $P<0.05$ for all statistical tests and corrected for multiple comparisons when necessary. All statistical analysis will be performed using SPSS software (version 13.0; SPSS Inc., Chicago, IL, USA).

Quality control and quality assurance

3 senior neurologists will jointly evaluate each patient's stroke status through reading his record during patient recruitment. The experimental data will be reviewed and verified by a senior researcher.

Patient and public involvement

The initial research idea was conceived by the authors and modified according to the face-to-face interviews to stroke patients and their guardians. Before the formal experiment, 5 stroke patients will be invited to practice the CCH and GRASP. The intervention protocols will be adjusted based on their comments and feedback to ensure the safety and applicability of the intervention. The burdens and potential benefits of the study will be fully explained to the patients and their guardians before signing the inform consent, and the study results will be released to them on request.

Ethics and dissemination

This study will be conducted in accordance with the principles of the Declaration of Helsinki. The ethics approvals have been obtained from the Research Ethics Committee of the Second Rehabilitation Hospital of Shanghai (Study ID: 2020-32-01, approved date: December 15, 2020) and the Shanghai University of Sport (Study ID: 102772021RT043, approved date: January 19, 2021). The authors will communicate with the recruited patients about the study information, including the study aims, the recruitment criteria, the study protocols, the potential risks, and the expected outcomes. The authors will

also provide direct consultation to all patients and their guardians to address any concerns they may encounter. The patients and their guardians will make the final decision to join or withdraw from the study. All the recruited patients will sign the informed consent before the study.

Patients' identifiable information will be stored separately from their clinical information and research data by one of the authors who take charge of the patient randomization. In order to protect patients' confidentiality, only the director of the study, this author, and the ethics committee will have access to the patients' personal information and medical records. At the end of the study, all the data will be input into a password-protected hard drive, and will be discarded 3 years after the study.

The results of the study will be published on peer-reviewed scientific journals and presented at conferences and workshops within 12 months after study completion. According to the instructions of the International Committee of Medical Journal Editors, individuals who meet the criteria for authorship will be included as authors of the publications. The CCH exercise and the corresponding equipment (copybook, calligraphy brush, etc.) will be optimized and promoted to the vast physiotherapists to enable the clinical transition.

Discussion and conclusion

The study was designed as a randomized controlled trial to evaluate the effect of the specially designed calligraphy exercise on the recovery of upper limb functions for patients after stroke. The results of the study will demonstrate the using of calligraphy therapy to enhance the continuity of recovery with daily practicing. Patients can independently execute the calligraphy exercise without the presence of a rehabilitation therapist, and therefore are able to maximize time spent improving their upper-limb function with a minimum financial expense.

Author statement

Xiaodi Wu: Perform the preliminary experiment; write the manuscript

Qiang Zhang: Design the experiment; write the manuscript (joined); edit the manuscript

Jun Qiao: Perform the preliminary experiment

Nan Chen: Supervise the experiment

Xie Wu: Design the experiment, be the PI of the project

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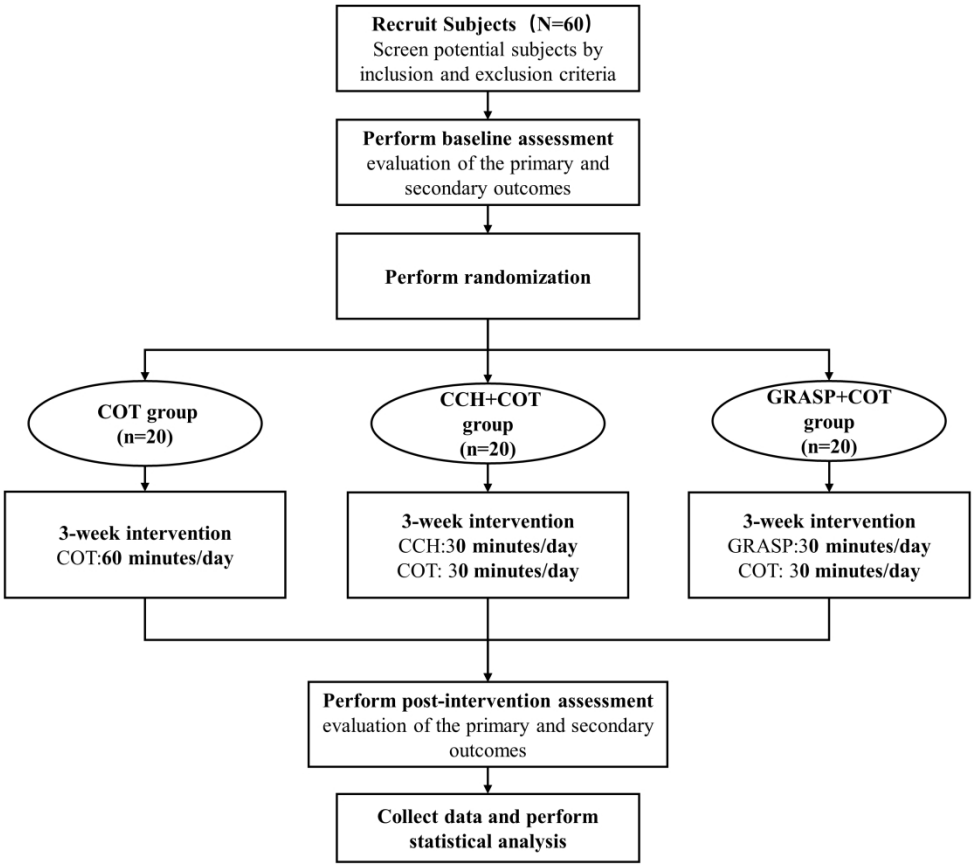

Figure 1. The study flowchart. COT, conventional occupational therapy; CCH, Chinese calligraphy handwriting; GRASP, Graded Repetitive Arm Supplementary Program.

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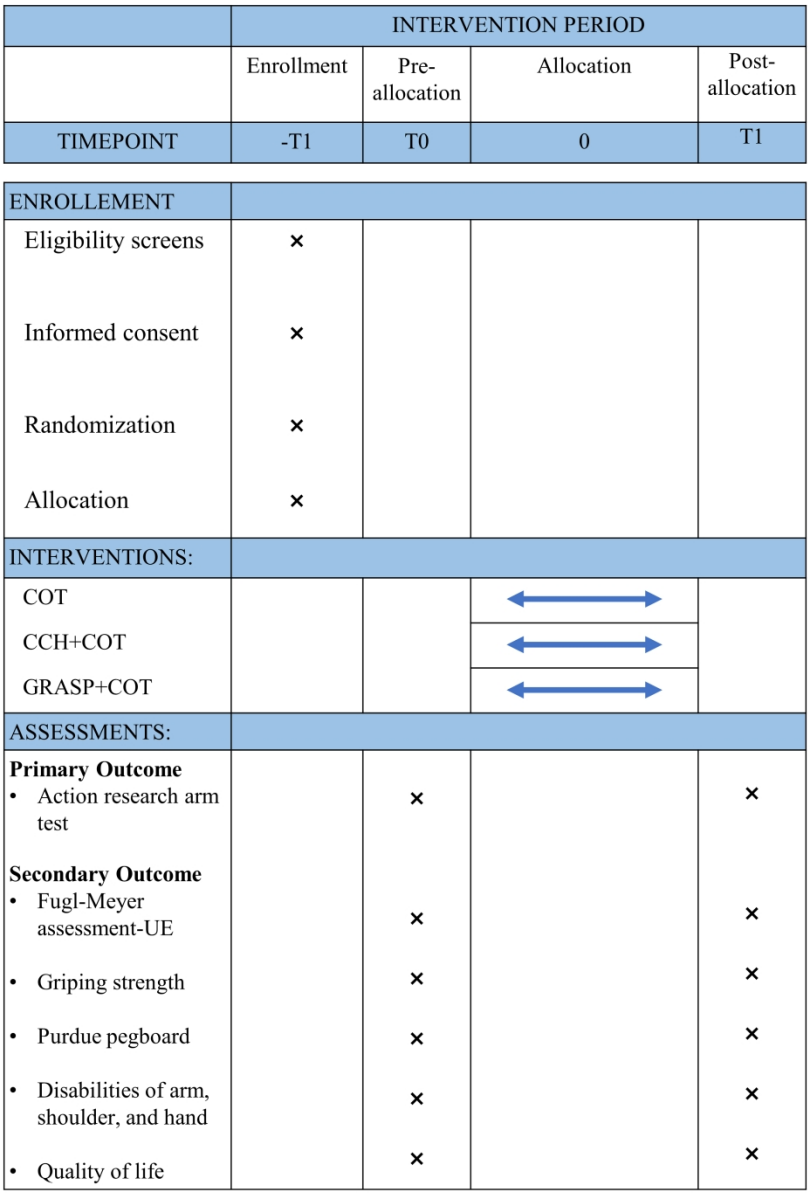

Figure 2. The experiment schedule, including patient enrollment, intervention progresses, and outcome assessments. Time points: -T1) before baseline screening; T0) baseline; T1) after intervention.

233x338mm (300 x 300 DPI)

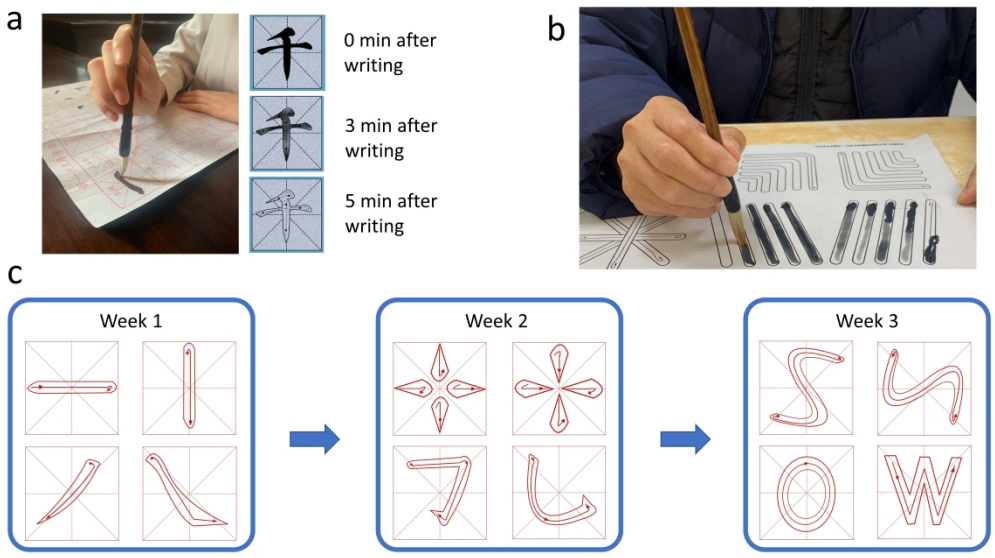

Figure 3. Calligraphy practicing and copybook design. a) Left: standard way of calligraphy handwriting; right: water drying out in 5 mins on the copybook. b) A patient is practicing the calligraphy handwriting. c) The difficulty of calligraphy practicing increases as the character frames become more complicated.

338x190mm (300 x 300 DPI)

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	10
	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)	10

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	4
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	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)	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	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)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	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)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	8
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)	7

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	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	8
	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	7

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	10
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	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	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)	9
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	9
	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	7
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	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
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)	9

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
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	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
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	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	NA
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	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Supplementary_
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	NA

*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.

上海体育学院科学研究伦理委员会

被试知情同意书

协议/研究题目	毛笔书法练习对脑卒中后上肢功能恢复效果的研究				
主要研究者	伍勰	电话	13564945511	Email	wuxia_sus@163.com
合作研究者	吴晓迪	电话	15221187792	Email	wuxiaodi1029@163.com
被试紧急联系人		电话			

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上海体育学院科学研究伦理委员会

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BMJ Open

A Calligraphy-based Rehabilitation Exercise for Improving the Upper-limb Function of Stroke Patients: Protocol for A Randomized Controlled Study

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A Calligraphy-based Rehabilitation Exercise for Improving the Upper-limb Function of Stroke Patients: Protocol for A Randomized Controlled Study

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Abstract

Introduction: A common complication of stroke is upper-limb dysfunction. Chinese calligraphy handwriting (CCH) is an aesthetical exercise developed from the traditional way of writing in China and holds potential to become a rehabilitation method to improve upper-limb functions in stroke patients. This study aims to design a randomized controlled trial to assess the effect of a customized CCH-based exercise for post-stroke rehabilitation of upper-limb dysfunction.

Methods and analysis: A single-blinded randomized controlled trial will be conducted on 60 stroke patients. The patients will be randomly allocated into three groups: 1) conventional occupational therapy (COT) group; 2) COT+CCH group; 3) COT+ Graded Repetitive Arm Supplementary Program (GRASP) group. For the COT group, patients will receive COT treatment of 1 hour per day. For the COT+CCH group, patients will receive 30-mins COT treatment and 30-mins CCH training. For the COT+GRASP group, patients will receive 30-mins COT treatment and 30-mins GRASP training. All the interventions will be performed 5 days per week for a total of 3 weeks. The upper-limb functions will be assessed before and after the interventions using a series of rating scales.

Ethics and dissemination: This study has been approved by the Research Ethics Committees of the Second Rehabilitation Hospital of Shanghai (Study ID: 2020-32-01) and the Shanghai University of Sport (Study ID: 102772021RT043). Results will be directly disseminated to the patients at the end of the study, and to the public via publications in peer-reviewed journals and presentations in conferences.

Trial registration number: Chinese Clinical Trials Registry (ChiCTR 2100043036)

Keywords: Rehabilitation; Stroke; Calligraphy; Upper limb function; Protocol; Motor control

Article summary

Strengths and limitations of this study

- This study will be the first randomized controlled trial to explore the effects of Chinese calligraphy handwriting in regard to facilitate hemiparetic upper limb recovery in stroke patients.
- The Chinese Calligraphy is a culture-based self-performed exercise with minimized risk so that patients can continue to perform this exercise after returning home from the hospital.
- This study is single-blind study. Patients and therapist delivering the intervention cannot be blinded to the intervention allocation, which potentially introduces a source of bias.

Introduction

Recent epidemiological studies have revealed that each year near 17 million people suffer from stroke in the world [1-3], and in China alone over 2.5 million new stroke cases are diagnosed per year [3, 4]. With the improved care in the hyperacute and acute periods of stroke, around 80% of stroke patients can survive from the initial injuries [5]. However, stroke can usually lead to severe neuropsychiatric disorders in patients, such as motion capacities, sensory, and cognitive impairments [6, 7]. As one of the most common complications, the motor impairment might affect the unilateral movement abilities of patients' upper limbs [8, 9]. Patients with such upper-limb dysfunctions would exhibit difficulties in contracting muscles, as well as in the control and coordination of their arms, hands, and fingers. The post-stroke upper-limb dysfunctions can thus limit the patients in daily activities such as eating, dressing, and washing [10-12], and increase their dependences and affect the quality of life in a long time period [13]. Therefore, post-stroke rehabilitation of upper-limb dysfunction is critical in restoring patients' upper-limb functions and improving their quality of life [14].

By leveraging different technologies, multiple post-stroke rehabilitation therapies have been developed and used to restore upper-limb functions, such as therapist-assisted practice [15-17], bilateral training [18], constraint-induced movement therapy (CIMT) [19], robotic-assisted therapy [20], mirror therapy [21], and virtual reality [22]. As the function recovery can last into the chronic phase of stroke [23], there is an increasing interest in validating interventions that aim to enhance the physical and psychological well-being in both acute and chronic periods of post-stroke rehabilitation. It is recognized that therapies involving high-intensity repetitive tasks, such as the CIMT, have the best effect on the recovery of upper-limb functions [8]. However, by limiting the contralateral arm the CIMT forces the patient to use the impaired arm, and thus challenges the patient's compliance during therapy [19, 24] so that treatment outcomes are compromised [25, 26]. Therefore, high-intensity repetitive therapies might not be optimal for long-term rehabilitation of post-stroke upper-limb dysfunctions as well as for the improvement of the psychological well-being of the patients. The therapies supervised by therapists or with sophisticated equipment can increase the financial pressure of the patients [27, 28], and thus might not be widely accepted for long-term persistence. Therefore, economical and easy-to-adherence interventive exercises should be developed and

involved to current post-stroke rehabilitation programs to allow the patients to persist in the training to obtain ongoing benefits from the therapy.

Chinese calligraphy handwriting (CCH) is a culture-based exercise to express the aesthetics of Chinese characters and writers' inner psyche [29]. Clinically, the CCH process has been suggested to facilitate people's psychosomatic and cognitive wellbeing [30], and to exert curative effects on autism, depression, and posttraumatic stress disorder [29]. For example, it was reported that CCH could improve specific cognitive functions in patients with mild cognitive impairment [31]. It was also suggested that CCH could stabilize physiological arousal parameters of cancer survivors, including slower heart rate, decreased blood pressure, and decelerated respiration [32]. Thus, the CCH might also be able to mitigate post-stroke neuropsychiatric disorders.

The CCH may be a proper exercise to improve stroke patients' upper limbs functions because of its unique writing styles. First, long-term CCH training might facilitate the neuroplasticity in human brain [33]. In this study, the cingulate gyrus area was found to be relatively small in people who had practiced calligraphy for over 5 years, which was possibly due to increased efficiency of cingulate gyrus neuron utilization. The CCH involves dynamic feedforward and feedback between visuo-perceptual, proprioception, and upper-limb motor system [34]. Specifically, the writer first predicts and plans the size and positions of each character on the paper. During CCH, the writer needs to recall the planned configurations of the characters and compare them to the writings. Such visual feedback on the writings also forces the writer to adjust brush gripping, applied pressure, and writing speed. As the main function of the cingulate neurons is the pre-visual stimulation and pre-motor planning, the CCH might stimulate the cingulate neurons in the brain. Therefore, the CCH may be able to improve the patient's cognitive well-being, hand-eye coordination, and real-time execution ability [34]. Second, the writer needs to maintain the upper-limb stability to smoothen the thickness of the character strokes during CCH, which may effectively stimulate muscle contractions in the upper limb. Third, the writer strives to control the writing speed and frequently alters the tilt angles during writing. Therefore, performing the CCH may be able to train coordinative movements and improve the flexibility of upper-limb joints. As a consequence, the CCH holds great potential not only in facilitating the recovery of upper-limb functions but also in improving the mental state of stroke patients.

The cultural factors behind the CCH may make it more easily accepted by Chinese patients than many

other exercises. Calligraphy copybook is prevalently used at the beginning of CCH self-practicing because the character frames in the copybook can regulate people's writing styles without the need of instructors. Thus, the calligraphy copybook may be an excellent tool for stroke patients to practice the CCH exercise at both hospital and home. In addition to Chinese characters, the copybook can also be designed by including characters of other languages to make it more suitable for patients with other cultural backgrounds. Therefore, the purpose of this study is to develop a CCH-based interventive exercise with a self-designed calligraphy copybook and validate its effect on the improvement of patients' upper-limb functions in the chronic period of stroke.

Methods

Study design

This study will be a single-center, three-arm, parallel group, assessors-blind randomized controlled trial. All the patients will be informed of the study content before the subject recruitment. The patients who meet the inclusion criteria and agree to participate in the study will sign the informed consent. As shown in the study flow chart (Fig. 1), the patients will be randomly allocated into 3 groups with equal sample size: 1) conventional occupational therapy (COT) group; 2) COT+CCH group; 3) COT+ Graded Repetitive Arm Supplementary Program (GRASP) group. The rehabilitation interventions will last 3 weeks. Patients' upper-limb functions will be assessed using rating scales before and after the interventions. The study protocol is shown in Fig. 2 (recommended for interventional trials (SPIRIT) 2013) [35].

[Insert Fig. 1 here]

[Insert Fig. 2 here]

Subject recruitment and randomization

From January 2021 to September 2021, patients will be screened and recruited in the Department of Neurological Rehabilitation in the Second Rehabilitation Hospital of Shanghai via reviewing their electronic medical records. This study will only recruit patients who meet the following criteria: 1) first-ever stroke through neuroimaging assessment; 2) within the chronic phase of stroke; 3) able to sit without upper-limb supporting; 4) sufficient active range of motion: 90° of shoulder flexion, 90° of elbow flexion, 30° of wrist pronation/supination, 30° of wrist flexion; 5) able to hold the calligraphy brush with the affected hand; 6) good cognitive ability (Mini-Mental State Exam scores > 23) [36]; 7) no serious visual impairment or visual field defect; 8) 40-80 years old. The exclusion criteria of this study include: 1) other neurological diseases or upper-limb surgical histories; 2) severe communication deficits; 3) obvious shoulder pain (pain rating at rest > 5) [37].

Subject randomization will be performed by an external professional statistician. Number 1-60 will be randomly sequenced using the SPSS V.23.0. 60 envelopes will be prepared, each with an external series number corresponding to the random sequence generated and an internal group number: #1 (COT group),

#2 (COT+CCH group), or #3 (COT+GRASP group) [38]. Once a patient is recruited, the authors will open an envelope sequentially and allocate the patient into a group according to the internal group number. The external series number on the envelope will also be used as the ID of each patient to track their information and data throughout the entire study, which makes the assessor blind to the group allocation.

Sample size

According to a previous study [39], the minimal clinical important difference for the Action Research Arm Test scale is 6 in patients with chronic stroke. The mean score that patients with chronic stroke can achieve was reported to be about 30 [40]. Thus, the effect size is estimated to be 0.2. The sample size was then calculated using this value in G*Power 3 (Erdfelder, Faul, & Buchner, 1996). To achieve a power of 80% ($\alpha = 0.05$), a minimum of 18 subjects is required for each group. Taking this rate into consideration, a total of 60 patients (20 per group) will be recruited in the study.

Interventions

All patients will receive rehabilitation interventions based on routine treatment and daily nursing in the hospital. The rehabilitation interventions will be carried out 5 days per week for a total of 3 weeks.

In the COT group, the patients will receive 60-mins COT treatment five times per week. The treatment will be performed by a therapist, which comprises task-related practices for gross movements and dexterity, including different grips, selective finger movements, strength training, stretching, and daily life activities.

In the COT+CCH group, the patients will receive 30-mins COT treatment and 30-mins CCH training five times per week. The CCH training will be performed on self-designed copybooks with hollowed-out character frames (Fig. 3a). The copybooks are reusable as the water dries out in 5 minutes. During writing, the patients will be required to sit in front of a desk. The patients hold a calligraphy brush using the thumb, index finger, and middle finger of the affected hand, soak its head with water, and then fill the character frames on the copybook (Fig. 3b). Three different copybooks with increasing difficulties are designed, and each will be used in the CCH training for 1 week (Fig. 3c). This design can enable the patients to imitate geometric shapes, beginning with straight lines, followed by more complicated circles and curves, which will comply with the skill relearning progression within the post-stroke rehabilitation [41].

[Insert Fig. 3 here]

In the COT+GRASP group, the patients will receive 30-mins COT treatment and 30-mins GRASP training every day. The GRASP is a standardized post-stroke upper-limb rehabilitation program [42], and has been demonstrated to be effective in enhancing the motor function of the upper limb of chronic stroke patients [43]. The patients will perform GRASP by referring to an exercise manual presenting the schematic diagrams of each exercise. During the GRASP training, the therapist will leverage simple tools (such as balls, cups, and towels) to guide the patients to practice the actions and skills involved in daily activities [44].

Outcome assessment

The effects of these interventions on patients' upper-limb functions and quality of life will be assessed using a couple of different rating scales by a senior physiotherapist with over 5-years of relevant experience. This physiotherapist will not be involved in the execution of the intervention and will remain blinded to the group of the patient during the entire trial. To ensure maximum blindness, the patients will also be requested not to discuss their intervention exercises with the physiotherapist during the assessment. The rating scales include:

1) Primary outcome measures

- Action Research Arm Test (ARAT) [45]: The measure is a 19-items test divided into 4 subtests (grasp, grip, pinch and gross movement). For each item, the patient is asked to perform a simple task that involves a functional movement of the affected upper limb. The details of each scale can be found in the supplementary material.

2) Secondary outcome measures

- Fugl-Meyer assessment-UE (FMA-UE) [46]: This measure is designed to assess motor function, sensation, balance, range of motion, and joint pain.
- Griping strength of the affected hand will be measured as the mean of 3 consecutive trials.
- Purdue pegboard (PPB) [47]: The PPB is a reliable measure to assess the gross movement of the arm, hand and fingers, as well as the fingertip dexterity. This measure requires patients to

pick up pins one at a time and place them in a row of holes.

- Disabilities of arm, shoulder, and hand (DASH) [48]: This measure is a 30-item self-report questionnaire, which is designed to assess individually rated upper limb impairments and impacts on activities for patients with musculoskeletal conditions in the upper limbs.

- Quality of life (short form 36, SF-36) [49]: This measure is a generic self-report of health status for evaluating the quality of life that relates to physical and mental well-being.

Statistical method

Two-way analysis of variance (ANOVA) will be applied to examine the interaction and the main effects of the intervention method and the assessment time. 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. If significant interaction is found, Tukey *post hoc* tests will be performed. Demographic characteristics and other baseline values will be described using descriptive statistics for each group. Significant level for all tests will be set at $P<0.05$ for all statistical tests and corrected for multiple comparisons using the Bonferroni method. All statistical analysis will be performed using SPSS (version 13.0; SPSS Inc., Chicago, IL, USA).

Quality control and quality assurance

During patient recruitment, 3 senior neurologists will jointly evaluate each patient's stroke status based on his medical record. The experimental data will be reviewed and verified by a senior researcher.

Management of adverse events

Possible adverse events include shoulder pain, hand soreness and numbness, and muscle fatigue. The patients will be instructed to rate and report the severity of pain and fatigue from 0 (e.g., no pain) to 10 (e.g., unbearable pain) at the end of each treatment. The research team will record the adverse event, including duration, severity, and position. If any patient reports severe adverse events that may affect the progressing of the intervention, the test will be paused, and relieving treatment will be provided. If the symptom cannot be relieved, the intervention will be terminated.

Patient and public involvement

The initial research idea was conceived by the authors and modified according to face-to-face interviews with stroke patients and their guardians. Before the formal experiment, 5 stroke patients will be invited to practice the CCH and GRASP. The intervention protocols will be adjusted based on their feedback to ensure the safety and applicability of the intervention. The potential risks and benefits of the study will be fully explained to the patients and their guardians before signing the informed consent, and the study results will be released to them on request.

Ethics and dissemination

This study will be conducted in accordance with the principles of the Declaration of Helsinki. The ethics approvals have been obtained from the Research Ethics Committee of the Second Rehabilitation Hospital of Shanghai (Study ID: 2020-32-01, approved date: December 15, 2020) and the Shanghai University of Sport (Study ID: 102772021RT043, approved date: January 19, 2021). The authors will communicate the study information, including the study aims, the recruitment criteria, the study protocols, the potential risks, and the expected outcomes to the recruited patients. The authors will provide direct consultation to all patients and their guardians to address any concerns they may encounter. The patients and their guardians will make the final decision to join or withdraw from the study. All the recruited patients will sign the informed consent before the study.

Patients' identifiable information will be stored separately from their clinical information and research data by one of the authors who is in charge of the patient randomization. In order to protect patients' confidentiality, only the director of the study, this author, and the ethics committee will have access to the patients' personal information and medical records. At the end of the study, the data will be saved on a password-protected hard drive, and will be discarded 3 years after the study.

The results of the study will be published in peer-reviewed scientific journals and presented at conferences and workshops within 12 months after study completion. According to the instructions of the International Committee of Medical Journal Editors, individuals who meet the criteria for authorship will be included as authors of the publications. The CCH exercise and the corresponding equipment (copybook, calligraphy brush, etc.) will be optimized and promoted to the vast physiotherapists to enable the clinical

transition.

Discussion and conclusion

The study was designed as a randomized controlled trial to evaluate the effect of the specially designed calligraphy exercise on the recovery of upper limb functions in stroke patients. The results of the study will demonstrate that calligraphy therapy enhances the continuity of recovery with daily practicing. Patients can independently execute the calligraphy exercise without the presence of a rehabilitation therapist, and therefore are able to maximize time spent improving their upper-limb function with a minimum financial expense.

Author statement

Xiaodi Wu: Perform the preliminary experiment; write the manuscript

Qiang Zhang: Design the experiment; write the manuscript (joined); edit the manuscript

Jun Qiao: Perform the preliminary experiment

Nan Chen: Supervise the experiment

Xie Wu: Design the experiment, be the PI of the project

Titles of figures

Figure 1. The study flowchart. COT, conventional occupational therapy; CCH, Chinese calligraphy handwriting; GRASP, Graded Repetitive Arm Supplementary Program.

Figure 2. The experiment schedule, including patient enrollment, intervention progresses, and outcome assessments. The schedule was developed according to the standard protocol project statement for randomized trials. Time points: -T1) before baseline screening; T0) baseline; T1) after intervention.

Figure 3. Calligraphy practicing and copybook design. a) Left: standard way of calligraphy handwriting; right: water drying out in 5 mins on the copybook. b) A patient is practicing the calligraphy handwriting. c) The difficulty of calligraphy practicing increases as the character frames become more complicated.

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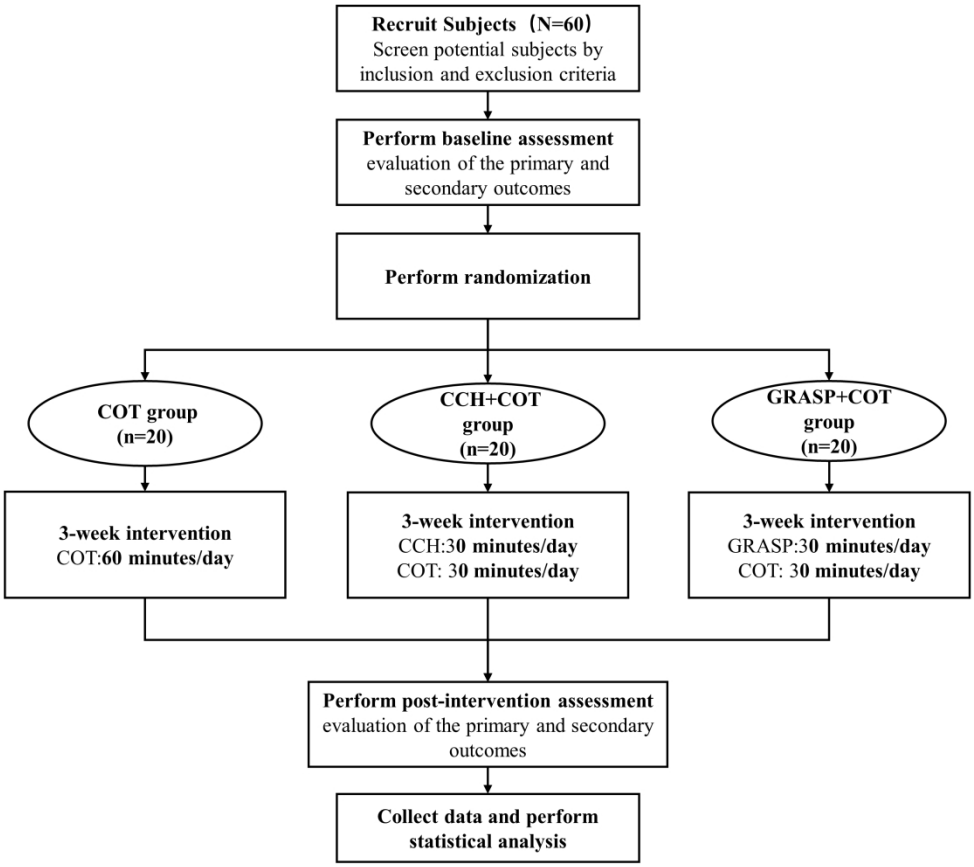

Figure 1. The study flowchart. COT, conventional occupational therapy; CCH, Chinese calligraphy handwriting; GRASP, Graded Repetitive Arm Supplementary Program.

240x209mm (300 x 300 DPI)

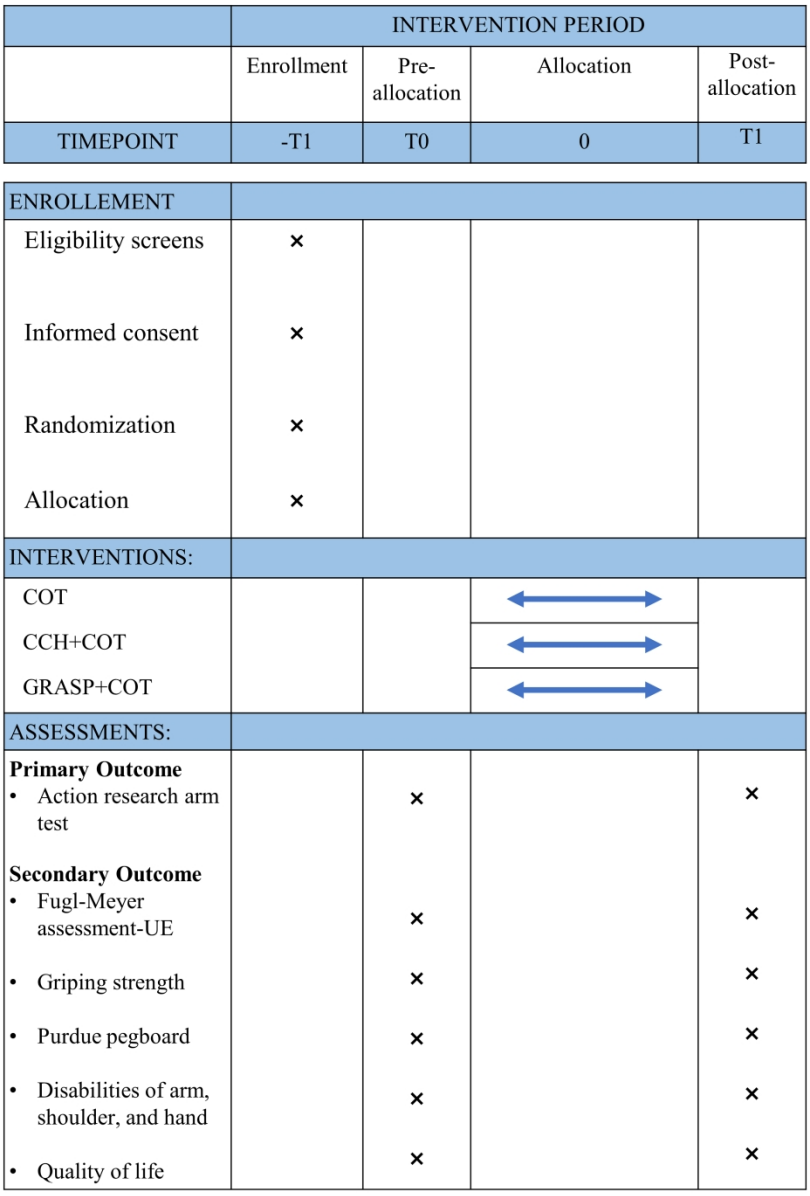

Figure 2. The experiment schedule, including patient enrollment, intervention progresses, and outcome assessments. Time points: -T1) before baseline screening; T0) baseline; T1) after intervention.

233x338mm (300 x 300 DPI)

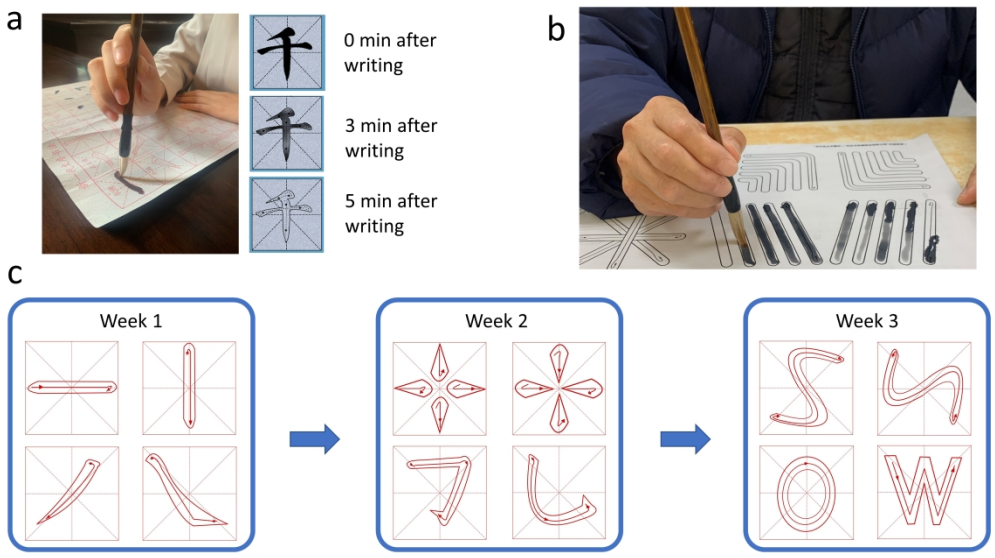

Figure 3. Calligraphy practicing and copybook design. a) Left: standard way of calligraphy handwriting; right: water drying out in 5 mins on the copybook. b) A patient is practicing the calligraphy handwriting. c) The difficulty of calligraphy practicing increases as the character frames become more complicated.

338x190mm (300 x 300 DPI)

Supplementary of:

A Calligraphy-based Rehabilitation Exercise for Improving the Upper-limb Function of Stroke Patients: Protocol for A Randomized Controlled Study

Xiaodi Wu[*], *Qiang Zhang*[*], *Jun Qiao, Nan Chen*[#], *Xie Wu*[#]

Below describes the details of the rating scales that will be used in the experiment:

1) Primary outcome measures

- Action Research Arm Test (ARAT): The ARAT was developed by Lyle in 1981 to measure function of the arm and hand in a variety of tasks, with special focus on fine motor function of hands. all 19 items of the ARAT are scored on a 4-point scale (0-3). Scores are judged as follows. 0, the patient is unable to perform any part of the task; 1, the patient is able to completely lift the object from the flat platform; 2, the function is completely completed but is very clumsy or very difficult; and 3, the movement is completed normally. The scores for each item were calculated by summing the total score for each side, ranging from 0 to 57 [1]. In addition, the overall time for patient to complete the ARAT will be recorded. The ARAT has good predictive and concurrent validity [2].

2) Secondary outcome measures

- Fugl-Meyer assessment-UE (FMA-UE): The FMA was designed in 1975 as a global assessment index for quantitative assessment of recovery of post-stroke paraplegic limbs. It is a quantitative performance-based measure consisting of 33 items that measure motor function of the upper limb. Each item is scored on a 3-point scale (0=can't perform, 1=can partially perform, 2=can fully perform), and the maximum score is 66. The severe degree of paresis was distributed according to the FMA score as follows. ≤25 points: severe, 26 to 45 points: moderate, and 46 to 66 points: mild [3]. The FMA has a high inter-rater and test-reset reliability [4].

- Griping strength of the affected hand: The grip force of the affected hand was measured with a dynamometer (Xiangshan, EH-101). The patient insisted the griping at his/her best for three seconds, and then rested for 30 s. The test was performed three times, and the maximum value was recorded.

- Purdue pegboard (PPB): The PPB was developed by Tiffin in 1948 to measure gross motor skill in the use of the arm, hand, and fingers, as well as fingertip dexterity. It consists of five subtests: dominant hand (D), non-dominant hand (ND), both hands (B), dominant +non-dominant+ both hands (D+ND+B), and an assembly subtest. In the five subtests, very small pins, washers, and collars were manipulated with one and two hands, and participants were

asked to place as many pins as possible into the holes within 30 seconds. In subtests D, ND, and B, the number of pins placed within 30 s was recorded. scores for subtests D+ND+B could be calculated from the scores of the first three tests. The assembly subtest score is the total number of pins, washers, and collars placed in 60 s [5]. PPB has good predictive and concurrent validity [6].

- Disabilities of arm, shoulder, and hand (DASH) : DASH is a 30-item self-report questionnaire designed to assess individual ratings of upper limb impairment and effects on activity in patients with upper limb musculoskeletal disorders. The items ask about the level of difficulty in performing different physical activities due to upper limb problems (21 items), the severity of symptoms such as upper limb pain, weakness and stiffness (5 items), and the impact of the problem on social activity participation, etc. (4 items). Each item has five options for response, with scores ranging from 0 (no disability) to 100 (most severe disability), with higher scores indicating greater disability. DASH has good internal consistency and validity in adults following stroke [7].
- Quality of life (short form 36, SF-36) : SF-36 was normalized in 1990 as a self-report measure of functional health and well-being. The SF-36 consists of eight health scales. Physical Functioning (10 items), Role Limitation-Physical (4 items), Physical Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role Limitation-Emotional (3 items), and Mental Health (5 items). A score from 0 (the worst health measure) to 100 (the best health measure) was calculated for each scale. SF-36 has good internal consistencies and group differences validity in stroke patients [8, 9].

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	10
	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)	10

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	4
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	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)	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	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)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	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)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	8
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)	7

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	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	8
	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	7

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	10
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	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	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)	9
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	9
	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	7
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	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
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)	9

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
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	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
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	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	NA
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	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary
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	NA

*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.

BMJ Open

A Calligraphy-based Rehabilitation Exercise for Improving the Upper-limb Function of Stroke Patients: Protocol for an Evaluator-blinded Randomized Controlled Trial

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A Calligraphy-based Rehabilitation Exercise for Improving the Upper-limb Function of Stroke Patients: Protocol for an Evaluator-blinded Randomized Controlled Trial

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Abstract

Introduction: A common complication of stroke is upper-limb dysfunction. Chinese calligraphy handwriting (CCH) is an aesthetical exercise developed from the traditional way of writing in China and holds potential to become a rehabilitation method to improve upper-limb functions in stroke patients. This study aims to design a randomized controlled trial to assess the effect of a customized CCH-based exercise for post-stroke rehabilitation of upper-limb dysfunction.

Methods and analysis: A single-blinded randomized controlled trial will be conducted on 60 stroke patients. The patients will be randomly allocated into three groups: 1) conventional occupational therapy (COT) group; 2) COT+CCH group; 3) COT+ Graded Repetitive Arm Supplementary Program (GRASP) group. For the COT group, patients will receive COT treatment of 1 hour per day. For the COT+CCH group, patients will receive 30-mins COT treatment and 30-mins CCH training. For the COT+GRASP group, patients will receive 30-mins COT treatment and 30-mins GRASP training. All the interventions will be performed 5 days per week for a total of 3 weeks. The upper-limb functions will be assessed before and after the interventions using a series of rating scales.

Ethics and dissemination: This study has been approved by the Research Ethics Committees of the Second Rehabilitation Hospital of Shanghai (Study ID: 2020-32-01) and the Shanghai University of Sport (Study ID: 102772021RT043). Results will be directly disseminated to the patients at the end of the study, and to the public via publications in peer-reviewed journals and presentations in conferences.

Trial registration number: Chinese Clinical Trials Registry (ChiCTR 2100043036)

Keywords: Rehabilitation; Stroke; Calligraphy; Upper limb function; Protocol; Motor control

Article summary

Strengths and limitations of this study

- In this study, the efficacy of the proposed self-administrated CCH exercise will be compared with that of the popular GRASP, which will strengthen the convincingness of the outcomes.
- Outcome measures will include not only the performance of affected arm in various activities, but also the ability to use the affected arm for daily living will be evaluated using questionnaires.
- The overall time to complete the Action Research Arm Test will be measured and analyzed to reduce the ceiling effect.
- This study is evaluator-blinded study, and thus patients and therapists will not be blinded to the intervention allocation.
- This study has a short intervention period, and the long-term efficacy of CCH for improving poststroke upper-limb functions will not be investigated.

Introduction

Recent epidemiological studies have revealed that each year near 17 million people suffer from stroke in the world [1-3], and in China alone over 2.5 million new stroke cases are diagnosed per year [3, 4]. With the improved care in the hyperacute and acute periods of stroke, around 80% of stroke patients can survive from the initial injuries [5]. However, stroke can usually lead to severe neuropsychiatric disorders in patients, such as motion capacities, sensory, and cognitive impairments [6, 7]. As one of the most common complications, the motor impairment might affect the unilateral movement abilities of patients' upper limbs [8, 9]. Patients with such upper-limb dysfunctions would exhibit difficulties in contracting muscles, as well as in the control and coordination of their arms, hands, and fingers. The post-stroke upper-limb dysfunctions can thus limit the patients in daily activities such as eating, dressing, and washing [10-12], and increase their dependences and affect the quality of life in a long time period [13]. Therefore, post-stroke rehabilitation of upper-limb dysfunction is critical in restoring patients' upper-limb functions and improving their quality of life [14].

By leveraging different technologies, multiple post-stroke rehabilitation therapies have been developed and used to restore upper-limb functions, such as therapist-assisted practice [15-17], bilateral training [18], constraint-induced movement therapy (CIMT) [19], robotic-assisted therapy [20], mirror therapy [21], and virtual reality [22]. As the function recovery can last into the chronic phase of stroke [23], there is an increasing interest in validating interventions that aim to enhance the physical and psychological well-being in both acute and chronic periods of post-stroke rehabilitation. It is recognized that therapies involving high-intensity repetitive tasks, such as the CIMT, have the best effect on the recovery of upper-limb functions [8]. However, by limiting the contralateral arm the CIMT forces the patient to use the impaired arm, and thus challenges the patient's compliance during therapy [19, 24] so that treatment outcomes are compromised [25, 26]. Therefore, high-intensity repetitive therapies might not be optimal for long-term rehabilitation of post-stroke upper-limb dysfunctions as well as for the improvement of the psychological well-being of the patients. The therapies supervised by therapists or with sophisticated equipment can increase the financial pressure of the patients [27, 28], and thus might not be widely accepted for long-term persistence. Therefore, economical and easy-to-adherence interventive exercises should be developed and

involved to current post-stroke rehabilitation programs to allow the patients to persist in the training to obtain ongoing benefits from the therapy.

Chinese calligraphy handwriting (CCH) is a culture-based exercise to express the aesthetics of Chinese characters and writers' inner psyche [29]. Clinically, the CCH process has been suggested to facilitate people's psychosomatic and cognitive wellbeing [30], and to exert curative effects on autism, depression, and posttraumatic stress disorder [29]. For example, it was reported that CCH could improve specific cognitive functions in patients with mild cognitive impairment [31]. It was also suggested that CCH could stabilize physiological arousal parameters of cancer survivors, including slower heart rate, decreased blood pressure, and decelerated respiration [32]. Thus, the CCH might also be able to mitigate post-stroke neuropsychiatric disorders.

The CCH may be a proper exercise to improve stroke patients' upper limbs functions because of its unique writing styles. First, long-term CCH training might facilitate the neuroplasticity in human brain [33]. In this study, the cingulate gyrus area was found to be relatively small in people who had practiced calligraphy for over 5 years, which was possibly due to increased efficiency of cingulate gyrus neuron utilization. The CCH involves dynamic feedforward and feedback between visuo-perceptual, proprioception, and upper-limb motor system [34]. Specifically, the writer first predicts and plans the size and positions of each character on the paper. During CCH, the writer needs to recall the planned configurations of the characters and compare them to the writings. Such visual feedback on the writings also forces the writer to adjust brush gripping, applied pressure, and writing speed. As the main function of the cingulate neurons is the pre-visual stimulation and pre-motor planning, the CCH might stimulate the cingulate neurons in the brain. Therefore, the CCH may be able to improve the patient's cognitive well-being, hand-eye coordination, and real-time execution ability [34]. Second, the writer needs to maintain the upper-limb stability to smoothen the thickness of the character strokes during CCH, which may effectively stimulate muscle contractions in the upper limb. Third, the writer strives to control the writing speed and frequently alters the tilt angles during writing. Therefore, performing the CCH may be able to train coordinative movements and improve the flexibility of upper-limb joints. As a consequence, the CCH holds great potential not only in facilitating the recovery of upper-limb functions but also in improving the mental state of stroke patients.

The cultural factors behind the CCH may make it more easily accepted by Chinese patients than many

other exercises. Calligraphy copybook is prevalently used at the beginning of CCH self-practicing because the character frames in the copybook can regulate people's writing styles without the need of instructors. Thus, the calligraphy copybook may be an excellent tool for stroke patients to practice the CCH exercise at both hospital and home. In addition to Chinese characters, the copybook can also be designed by including characters of other languages to make it more suitable for patients with other cultural backgrounds. Therefore, the purpose of this study is to develop a CCH-based interventive exercise with a self-designed calligraphy copybook and validate its effect on the improvement of patients' upper-limb functions in the chronic period of stroke.

Methods

Study design

This study will be a single-center, three-arm, parallel group, assessors-blind randomized controlled trial. All the patients will be informed of the study content before the subject recruitment. The patients who meet the inclusion criteria and agree to participate in the study will sign the informed consent. As shown in the study flow chart (Fig. 1), the patients will be randomly allocated into 3 groups with equal sample size: 1) conventional occupational therapy (COT) group; 2) COT+CCH group; 3) COT+ Graded Repetitive Arm Supplementary Program (GRASP) group. The rehabilitation interventions will last 3 weeks. Patients' upper-limb functions will be assessed using rating scales before and after the interventions. The study protocol is shown in Fig. 2 (recommended for interventional trials (SPIRIT) 2013) [35].

[Insert Fig. 1 here]

[Insert Fig. 2 here]

Subject recruitment and randomization

From January 2021 to September 2021, patients will be screened and recruited in the Department of Neurological Rehabilitation in the Second Rehabilitation Hospital of Shanghai via reviewing their electronic medical records. This study will only recruit patients who meet the following criteria: 1) first-ever stroke through neuroimaging assessment; 2) within the chronic phase of stroke; 3) able to sit without upper-limb supporting; 4) sufficient active range of motion: 90° of shoulder flexion, 90° of elbow flexion, 30° of wrist pronation/supination, 30° of wrist flexion; 5) able to hold the calligraphy brush with the affected hand; 6) good cognitive ability (Mini-Mental State Exam scores > 23) [36]; 7) no serious visual impairment or visual field defect; 8) 40-80 years old. The exclusion criteria of this study include: 1) other neurological diseases or upper-limb surgical histories; 2) severe communication deficits; 3) obvious shoulder pain (pain rating at rest > 5) [37].

Subject randomization will be performed by an external professional statistician. Number 1-60 will be randomly sequenced using the SPSS V.23.0. 60 envelopes will be prepared, each with an external series number corresponding to the random sequence generated and an internal group number: #1 (COT group),

#2 (COT+CCH group), or #3 (COT+GRASP group) [38]. Once a patient is recruited, the authors will open an envelope sequentially and allocate the patient into a group according to the internal group number. The external series number on the envelope will also be used as the ID of each patient to track their information and data throughout the entire study, which makes the assessor blind to the group allocation.

Sample size

According to a previous study [39], the minimal clinical important difference for the Action Research Arm Test scale is 6 in patients with chronic stroke. The mean score that patients with chronic stroke can achieve was reported to be about 30 [40]. Thus, the effect size is estimated to be 0.2. The sample size was then calculated using this value in G*Power 3 (Erdfelder, Faul, & Buchner, 1996). To achieve a power of 80% ($\alpha = 0.05$), a minimum of 18 subjects is required for each group. Taking this rate into consideration, a total of 60 patients (20 per group) will be recruited in the study.

Interventions

All patients will receive rehabilitation interventions based on routine treatment and daily nursing in the hospital. The rehabilitation interventions will be carried out 5 days per week for a total of 3 weeks.

In the COT group, the patients will receive 60-mins COT treatment five times per week. The treatment will be performed by a therapist, which comprises task-related practices for gross movements and dexterity, including different grips, selective finger movements, strength training, stretching, and daily life activities.

In the COT+CCH group, the patients will receive 30-mins COT treatment and 30-mins CCH training five times per week. The CCH training will be performed on self-designed copybooks with hollowed-out character frames (Fig. 3a). The copybooks are reusable as the water dries out in 5 minutes. During writing, the patients will be required to sit in front of a desk. The patients hold a calligraphy brush using the thumb, index finger, and middle finger of the affected hand, soak its head with water, and then fill the character frames on the copybook (Fig. 3b). Three different copybooks with increasing difficulties are designed, and each will be used in the CCH training for 1 week (Fig. 3c). This design can enable the patients to imitate geometric shapes, beginning with straight lines, followed by more complicated circles and curves, which will comply with the skill relearning progression within the post-stroke rehabilitation [41].

[Insert Fig. 3 here]

In the COT+GRASP group, the patients will receive 30-mins COT treatment and 30-mins GRASP training every day. The GRASP is a standardized post-stroke upper-limb rehabilitation program [42], and has been demonstrated to be effective in enhancing the motor function of the upper limb of chronic stroke patients [43]. The patients will perform GRASP by referring to an exercise manual presenting the schematic diagrams of each exercise. During the GRASP training, the therapist will leverage simple tools (such as balls, cups, and towels) to guide the patients to practice the actions and skills involved in daily activities [44].

Outcome assessment

The effects of these interventions on patients' upper-limb functions and quality of life will be assessed using a couple of different rating scales by a senior physiotherapist with over 5-years of relevant experience. This physiotherapist will not be involved in the execution of the intervention and will remain blinded to the group of the patient during the entire trial. To ensure maximum blindness, the patients will also be requested not to discuss their intervention exercises with the physiotherapist during the assessment. The rating scales include:

1) Primary outcome measures

- Action Research Arm Test (ARAT) [45]: The measure is a 19-items test divided into 4 subtests (grasp, grip, pinch and gross movement). For each item, the patient is asked to perform a simple task that involves a functional movement of the affected upper limb. The details of each scale can be found in the supplementary material. In addition, upon evaluating the score that patients can achieve, the overall time for patient to complete the ARAT will also be measured, in order to reduce the potential ceiling effect [46].

2) Secondary outcome measures

- Fugl-Meyer assessment-UE (FMA-UE) [47]: This measure is designed to assess motor function, sensation, balance, range of motion, and joint pain.
- Griping strength of the affected hand will be measured as the mean of 3 consecutive trials.

- Purdue pegboard (PPB) [48]: The PPB is a reliable measure to assess the gross movement of the arm, hand and fingers, as well as the fingertip dexterity. This measure requires patients to pick up pins one at a time and place them in a row of holes.
- Disabilities of arm, shoulder, and hand (DASH) [49]: This measure is a 30-item self-report questionnaire, which is designed to assess individually rated upper limb impairments and impacts on activities for patients with musculoskeletal conditions in the upper limbs.
- Quality of life (short form 36, SF-36) [50]: This measure is a generic self-report of health status for evaluating the quality of life that relates to physical and mental well-being.

Statistical method

Two-way analysis of variance (ANOVA) will be applied to examine the interaction and the main effects of the intervention method and the assessment time. 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. If significant interaction is found, Tukey *post hoc* tests will be performed. Demographic characteristics and other baseline values will be described using descriptive statistics for each group. Significant level for all tests will be set at $P<0.05$ for all statistical tests and corrected for multiple comparisons using the Bonferroni method. All statistical analysis will be performed using SPSS (version 13.0; SPSS Inc., Chicago, IL, USA).

Quality control and quality assurance

During patient recruitment, 3 senior neurologists will jointly evaluate each patient's stroke status based on his medical record. The experimental data will be reviewed and verified by a senior researcher.

Management of adverse events

Possible adverse events include shoulder pain, hand soreness and numbness, and muscle fatigue. The patients will be instructed to rate and report the severity of pain and fatigue from 0 (e.g., no pain) to 10 (e.g., unbearable pain) at the end of each treatment. The research team will record the adverse event, including duration, severity, and position. If any patient reports severe adverse events that may affect the progressing of the intervention, the test will be paused, and relieving treatment will be provided. If the symptom cannot

be relieved, the intervention will be terminated.

Patient and public involvement

The initial research idea was conceived by the authors and modified according to face-to-face interviews with stroke patients and their guardians. Before the formal experiment, 5 stroke patients will be invited to practice the CCH and GRASP. The intervention protocols will be adjusted based on their feedback to ensure the safety and applicability of the intervention. The potential risks and benefits of the study will be fully explained to the patients and their guardians before signing the informed consent, and the study results will be released to them on request.

Ethics and dissemination

This study will be conducted in accordance with the principles of the Declaration of Helsinki. The ethics approvals have been obtained from the Research Ethics Committee of the Second Rehabilitation Hospital of Shanghai (Study ID: 2020-32-01, approved date: December 15, 2020) and the Shanghai University of Sport (Study ID: 102772021RT043, approved date: January 19, 2021). The authors will communicate the study information, including the study aims, the recruitment criteria, the study protocols, the potential risks, and the expected outcomes to the recruited patients. The authors will provide direct consultation to all patients and their guardians to address any concerns they may encounter. The patients and their guardians will make the final decision to join or withdraw from the study. All the recruited patients will sign the informed consent before the study.

Patients' identifiable information will be stored separately from their clinical information and research data by one of the authors who is in charge of the patient randomization. In order to protect patients' confidentiality, only the director of the study, this author, and the ethics committee will have access to the patients' personal information and medical records. At the end of the study, the data will be saved on a password-protected hard drive, and will be discarded 3 years after the study.

The results of the study will be published in peer-reviewed scientific journals and presented at conferences and workshops within 12 months after study completion. According to the instructions of the International Committee of Medical Journal Editors, individuals who meet the criteria for authorship will be included as authors of the publications. The CCH exercise and the corresponding equipment (copybook,

calligraphy brush, etc.) will be optimized and promoted to the vast physiotherapists to enable the clinical transition.

Discussion

The results of the study will demonstrate that CCH enhances the continuity of recovery with daily practicing. Many patients do not perform rehabilitation training at home after leaving the hospital due to financial burdens, and thus fail to further recover their upper-limb functions. The CCH is expected to become a home-based rehabilitation activity that can provide the patient with long-term benefits at low costs. Patients can independently execute the CCH exercise without the presence of a rehabilitation therapist, and therefore are able to maximize time spent improving their upper-limb function with a minimum financial expense. As a type of self-administrated exercise, the CCH may not be suitable for patients in the early stages of stroke recovery, but more suitable for patients who have initially benefited from hospital-based treatments and expect to continue upper-limb rehabilitations after leaving the hospital. Upon the completion of this study, future research should include the design of a special brush that will be much easier to be held by the patient with inferior hand functions, in order to allow more patients to practice CCH to get benefits at an earlier stage after stroke.

Author statement

Xiaodi Wu: Perform the preliminary experiment; write the manuscript

Qiang Zhang: Design the experiment; write the manuscript (joined); edit the manuscript

Jun Qiao: Perform the preliminary experiment

Nan Chen: Supervise the experiment

Xie Wu: Design the experiment, be the PI of the project

Titles of figures

Figure 1. The study flowchart. COT, conventional occupational therapy; CCH, Chinese calligraphy handwriting; GRASP, Graded Repetitive Arm Supplementary Program.

Figure 2. The experiment schedule, including patient enrollment, intervention progresses, and outcome assessments. The schedule was developed according to the standard protocol project statement for randomized trials. Time points: -T1) before baseline screening; T0) baseline; T1) after intervention.

Figure 3. Calligraphy practicing and copybook design. a) Water drying out in 5 mins on the copybook. b) A patient is practicing the calligraphy handwriting. c) The difficulty of calligraphy practicing increases as the character frames become more complicated.

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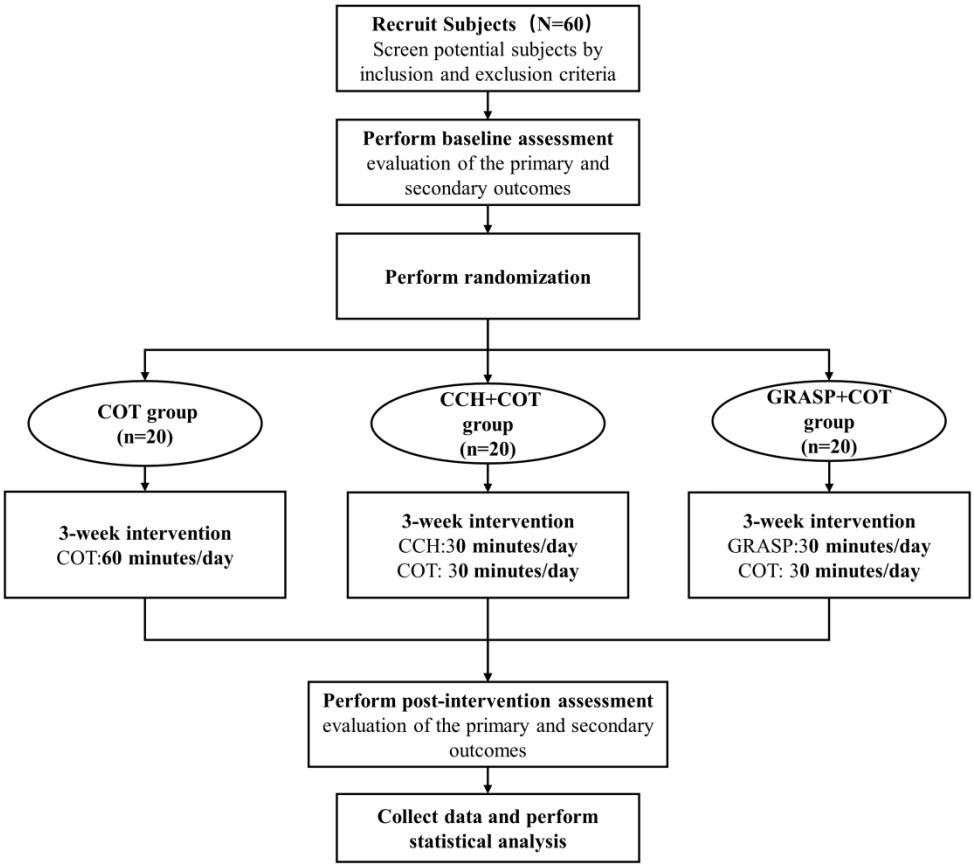

Figure 1. The study flowchart. COT, conventional occupational therapy; CCH, Chinese calligraphy handwriting; GRASP, Graded Repetitive Arm Supplementary Program.

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	INTERVENTION PERIOD			
	Enrollment	Pre-allocation	Allocation	Post-allocation
TIMEPOINT	-T1	T0	0	T1
ENROLLEMENT				
Eligibility screens	×			
Informed consent	×			
Randomization	×			
Allocation	×			
INTERVENTIONS:				
COT			⟷	
CCH+COT			⟷	
GRASP+COT			⟷	
ASSESSMENTS:				
Primary Outcome				
• Action research arm test		×		×
Secondary Outcome				
• Fugl-Meyer assessment-UE		×		×
• Griping strength		×		×
• Purdue pegboard		×		×
• Disabilities of arm, shoulder, and hand		×		×
• Quality of life		×		×

Figure 2. The experiment schedule, including patient enrollment, intervention progresses, and outcome assessments. Time points: -T1) before baseline screening; T0) baseline; T1) after intervention.

233x338mm (300 x 300 DPI)

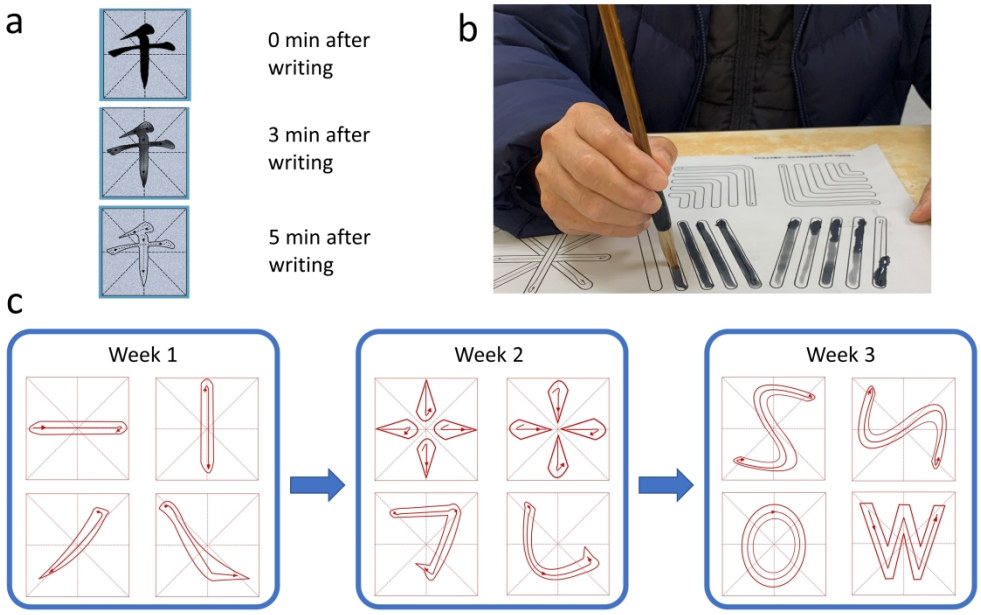

Figure 3. Calligraphy practicing and copybook design. a) Water drying out in 5 mins on the copybook. b) A patient is practicing the calligraphy handwriting. c) The difficulty of calligraphy practicing increases as the character frames become more complicated.

307x190mm (300 x 300 DPI)

Supplementary of:

A Calligraphy-based Rehabilitation Exercise for Improving the Upper-limb Function of Stroke Patients: Protocol for A Randomized Controlled Study

Xiaodi Wu[*], *Qiang Zhang*[*], *Jun Qiao, Nan Chen*[#], *Xie Wu*[#]

Below describes the details of the rating scales that will be used in the experiment:

1) Primary outcome measures

- Action Research Arm Test (ARAT): The ARAT was developed by Lyle in 1981 to measure function of the arm and hand in a variety of tasks, with special focus on fine motor function of hands. all 19 items of the ARAT are scored on a 4-point scale (0-3). Scores are judged as follows. 0, the patient is unable to perform any part of the task; 1, the patient is able to completely lift the object from the flat platform; 2, the function is completely completed but is very clumsy or very difficult; and 3, the movement is completed normally. The scores for each item were calculated by summing the total score for each side, ranging from 0 to 57 [1]. In addition, the overall time for patient to complete the ARAT will be recorded. The ARAT has good predictive and concurrent validity [2].

2) Secondary outcome measures

- Fugl-Meyer assessment-UE (FMA-UE): The FMA was designed in 1975 as a global assessment index for quantitative assessment of recovery of post-stroke paraplegic limbs. It is a quantitative performance-based measure consisting of 33 items that measure motor function of the upper limb. Each item is scored on a 3-point scale (0=can't perform, 1=can partially perform, 2=can fully perform), and the maximum score is 66. The severe degree of paresis was distributed according to the FMA score as follows. ≤25 points: severe, 26 to 45 points: moderate, and 46 to 66 points: mild [3]. The FMA has a high inter-rater and test-reset reliability [4].

- Griping strength of the affected hand: The grip force of the affected hand was measured with a dynamometer (Xiangshan, EH-101). The patient insisted the griping at his/her best for three seconds, and then rested for 30 s. The test was performed three times, and the maximum value was recorded.

- Purdue pegboard (PPB): The PPB was developed by Tiffin in 1948 to measure gross motor skill in the use of the arm, hand, and fingers, as well as fingertip dexterity. It consists of five subtests: dominant hand (D), non-dominant hand (ND), both hands (B), dominant +non-dominant+ both hands (D+ND+B), and an assembly subtest. In the five subtests, very small pins, washers, and collars were manipulated with one and two hands, and participants were

asked to place as many pins as possible into the holes within 30 seconds. In subtests D, ND, and B, the number of pins placed within 30 s was recorded. scores for subtests D+ND+B could be calculated from the scores of the first three tests. The assembly subtest score is the total number of pins, washers, and collars placed in 60 s [5]. PPB has good predictive and concurrent validity [6].

- Disabilities of arm, shoulder, and hand (DASH) : DASH is a 30-item self-report questionnaire designed to assess individual ratings of upper limb impairment and effects on activity in patients with upper limb musculoskeletal disorders. The items ask about the level of difficulty in performing different physical activities due to upper limb problems (21 items), the severity of symptoms such as upper limb pain, weakness and stiffness (5 items), and the impact of the problem on social activity participation, etc. (4 items). Each item has five options for response, with scores ranging from 0 (no disability) to 100 (most severe disability), with higher scores indicating greater disability. DASH has good internal consistency and validity in adults following stroke [7].
- Quality of life (short form 36, SF-36) : SF-36 was normalized in 1990 as a self-report measure of functional health and well-being. The SF-36 consists of eight health scales. Physical Functioning (10 items), Role Limitation-Physical (4 items), Physical Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role Limitation-Emotional (3 items), and Mental Health (5 items). A score from 0 (the worst health measure) to 100 (the best health measure) was calculated for each scale. SF-36 has good internal consistencies and group differences validity in stroke patients [8, 9].

Reference

1. Zhao, J.L., et al., *Translation and Initial Validation of the Chinese Version of the Action Research Arm Test in People with Stroke.* Biomed Res Int, 2019. **2019**: p. 5416560.
2. Zhao, J.L., et al., *Inter-rater and Intra-rater Reliability of the Chinese Version of the Action Research Arm Test in People With Stroke.* Front Neurol, 2019. **10**: p. 540.
3. Woytowicz, E.J., et al., *Determining Levels of Upper Extremity Movement Impairment by Applying a Cluster Analysis to the Fugl-Meyer Assessment of the Upper Extremity in Chronic Stroke.* Arch Phys Med Rehabil, 2017. **98**(3): p. 456-462.
4. Hernandez, E.D., et al., *Intra- and inter-rater reliability of Fugl-Meyer Assessment of Upper Extremity in stroke.* J Rehabil Med, 2019. **51**(9): p. 652-659.
5. van Tuijl, J.H., Y.J. Janssen-Potten, and H.A. Seelen, *Evaluation of upper extremity motor function tests in tetraplegics.* Spinal Cord, 2002. **40**(2): p. 51-64.
6. Lee, P., et al., *The test-retest reliability and the minimal detectable change of the Purdue pegboard test in schizophrenia.* J Formos Med Assoc, 2013. **112**(6): p. 332-7.
7. Dalton, E., et al., *Validity, reliability and ease of use of the disabilities of arm, shoulder and hand questionnaire in adults following stroke.* Disabil Rehabil, 2017. **39**(24): p. 2504-2511.
8. Unalan, D., et al., *Comparison of SF-36 and WHOQOL-100 in patients with stroke.* Neurol India, 2008. **56**(4): p. 426-32.
9. Hobart, J.C., et al., *Quality of life measurement after stroke: uses and abuses of the SF-36.* Stroke, 2002. **33**(5): p. 1348-56.

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	10
	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)	10

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	4
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	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)	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	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)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	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)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
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	8
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)	7

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	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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	8
	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	7

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	10
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	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	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)	9
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	9
	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	7
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	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
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)	9

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
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	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
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	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	NA
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	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary
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	NA

*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.