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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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Manuscripts

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6 1 **A Calligraphy-based Rehabilitation Exercise for Improving the Upper-limb**
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9 2 **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 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

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44 **Article summary**

45 **Strengths and limitations of this study**

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

54 Introduction

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

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

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4 81 current post-stroke rehabilitation programs, in order to allow the patients to persist the training to obtain
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6 82 ongoing benefits from the therapy.
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8 83 Chinese calligraphy handwriting (CCH) is a culture-based exercise to express the aesthetics of Chinese
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10 84 characters and writer's inner psyche [29]. Clinically, the CCH process has been found to be able to facilitate
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12 85 people's psychosomatic and cognitive wellbeing [30], and exerts curative effects on autism, depression, and
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14 86 posttraumatic stress disorder [29]. For example, it was reported that CCH could improve specific cognitive
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16 87 functions of the patients with mild cognitive impairment [31]. It was also reported that CCH could normalize
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18 88 physiological arousal parameters of cancer survivors, including slower heart rate, decreased blood pressure,
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20 89 and decelerated respiration [32]. Thus, the CCH may be able to mitigate the post-stroke neuropsychiatric
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22 90 disorders. More importantly, the CCH may be a proper exercise to improve the stroke patients' upper limbs
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24 91 functions because of its unique writing styles. Firstly, the writer needs to maintain the upper-limb stability
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26 92 to smooth the thickness of character strokes during the CCH, which makes it an effect way to stimulate
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28 93 muscle contractions of the upper limb. Secondly, the writer strives to control the writing speed and
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30 94 frequently alter the tilt angles during writing. Performing the CCH thus may be able to train the coordinative
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32 95 movements and improve the flexibility of upper-limb joints. Finally, the writer needs to imagine the
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34 96 configurations of the characters (e.g. position, size), and perform writing while simultaneously recalling and
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36 97 retrieving the configurations, which may be able to improve the patient's cognitive well-being, hand-eye
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38 98 coordination, and real-time execution ability [33]. Therefore, the CCH holds great potentials in facilitating
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40 99 the recovery of upper-limb functions as well as improving the mental state of stroke patients.
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42 100 The cultural factors behind the CCH may make it more easily accepted by Chinese patients than many
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44 101 other exercises. Calligraphy copybook is prevalently used at the beginning of CCH self-practicing because
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46 102 the character frames in the copybook can regulate people's writing styles without the need of instructors.
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48 103 The calligraphy copybook thus is an excellent tool for the stroke patients to practice CCH exercise at both
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50 104 hospital and home. Therefore, the purpose of this study is to develop a CCH-based interventive exercise
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52 105 with self-designed calligraphy copybook and validate its effect on improving patients' upper-limb functions
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54 106 in the chronic period of stroke.
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109 **Methods**

110 **Study design**

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

120 **Subject recruitment and randomization**

121 From January 2021 to September 2021, patients will be screened and recruited among the Department
122 of Neurological Rehabilitation in the Second Rehabilitation Hospital of Shanghai via reviewing their
123 electronic medical records. This study will only recruit patients who meet the following criteria: 1) first-
124 ever stroke through neuroimaging assessment; 2) within the chronic phase of stroke; 3) able to sit without
125 upper-limb supporting; 4) sufficient active range of motion: 90° of shoulder flexion, 90° of elbow flexion,
126 30° of wrist pronation/supination, 30° of wrist flexion; 5) able to hold the calligraphy brush with the affected
127 hand; 6) good cognitive ability (Mini-Mental State Exam scores > 23) [35]; 7) no serious visual impairment
128 or visual field defect; 8) 40-80 years old. Patients won't be recruited if they have: 1) other neurological
129 diseases or upper-limb surgical histories; 2) severe communication deficits; 3) obvious shoulder pain (pain
130 rating at rest > 5) [36].

131 Subject randomization will be performed by an external professional statistician. Number 1-60 will be
132 randomly sequenced using the SPSS V.23.0. 60 envelopes will be prepared, each with an external series
133 number corresponding to the random sequence generated and an internal group number: #1 (COT group),
134 #2 (COT+CCH group), or #3 (COT+GRASP group) [37]. Once a patient is recruited, the authors will open
135 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].

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4 163 In the COT+GRASP group, the patients will receive 30-mins COT treatment and 30-mins GRASP
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6 164 training every day. The GRASP is a standardized post-stroke upper-limb rehabilitation program [40], and
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8 165 has been demonstrated effective in enhancing the motor function of the upper limb of chronic stroke patients
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10 166 [41]. with an exercise manual presenting the schematic diagrams of each exercise as well as exercise
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12 167 equipment. During the GRASP training, the therapist will leverage simple tools (such as balls, cups, and
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14 168 towel) to guide the patients to practice the actions and skills involved in daily activities [42].
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16 169 **Outcome assessment**

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19 170 The effects of these interventions on patients' upper-limb functions and quality of life will be assessed
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21 171 using a couple of different rating scales by a senior physiotherapist with over 5-years relevant experiences.

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23 172 The rating scales include:

24 25 173 1) Primary outcome measures

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28 174 • Action Research Arm Test (ARAT) [43]: The measure is a 19-items test divided into 4 subtests
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30 175 (grasp, grip, pinch and gross movement). For each item, the patient is asked to perform a simple
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32 176 task that involves a functional movement of the affected upper limb.

33 34 177 2) Secondary outcome measures

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36 178 • Fugl-Meyer assessment-UE (FMA-UE) [44]: This measure is designed to assess motor function,
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38 179 sensation, balance, range of motion, and joint pain.
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41 180 • Gripping strength of the affected hand will be measured as the mean of 3 consecutive trials.
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43 181 • Purdue pegboard (PPB) [45]: This is a reliable measure to assess the gross movement of the arm,
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45 182 hand and fingers, as well as the fingertip dexterity. This measure requires patients to pick up
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47 183 pins one at a time and place them in a row of hole.
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50 184 • Disabilities of arm, shoulder, and hand (DASH) [46]: This measure is a 30-item self-report
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52 185 questionnaire, which is designed to assess individually rated upper limb impairments and
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54 186 impacts on activities for patients with musculoskeletal conditions in the upper limbs.
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56 187 • Quality of life (short form 36, SF-36) [47]: This measure is a generic self-report of health status
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58 188 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 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 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

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4 216 also provide direct consultation to all patients and their guardians to address any concerns they may
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6 217 encounter. The patients and their guardians will make the final decision to join or withdraw from the study.
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8 218 All the recruited patients will sign the informed consent before the study.
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10 219 Patients' identifiable information will be stored separately from their clinical information and research
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12 220 data by one of the authors who take charge of the patient randomization. In order to protect patients'
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14 221 confidentiality, only the director of the study, this author, and the ethics committee will have access to the
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16 222 patients' personal information and medical records. At the end of the study, all the data will be input into a
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18 223 password-protected hard drive, and will be discarded 3 years after the study.
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20 224 The results of the study will be published on peer-reviewed scientific journals and presented at
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22 225 conferences and workshops within 12 months after study completion. According to the instructions of the
23
24 226 International Committee of Medical Journal Editors, individuals who meet the criteria for authorship will
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26 227 be included as authors of the publications. The CCH exercise and the corresponding equipment (copybook,
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28 228 calligraphy brush, etc.) will be optimized and promoted to the vast physiotherapists to enable the clinical
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30 229 transition.
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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.

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4 238 **Author statement**
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7 239 Xiaodi Wu: Perform the preliminary experiment; write the manuscript
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9
10 240 Qiang Zhang: Design the experiment; write the manuscript (joined); edit the manuscript
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12 241 Jun Qiao: Perform the preliminary experiment
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14
15 242 Nan Chen: Supervise the experiment
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17 243 Xie Wu: Design the experiment, be the PI of the project
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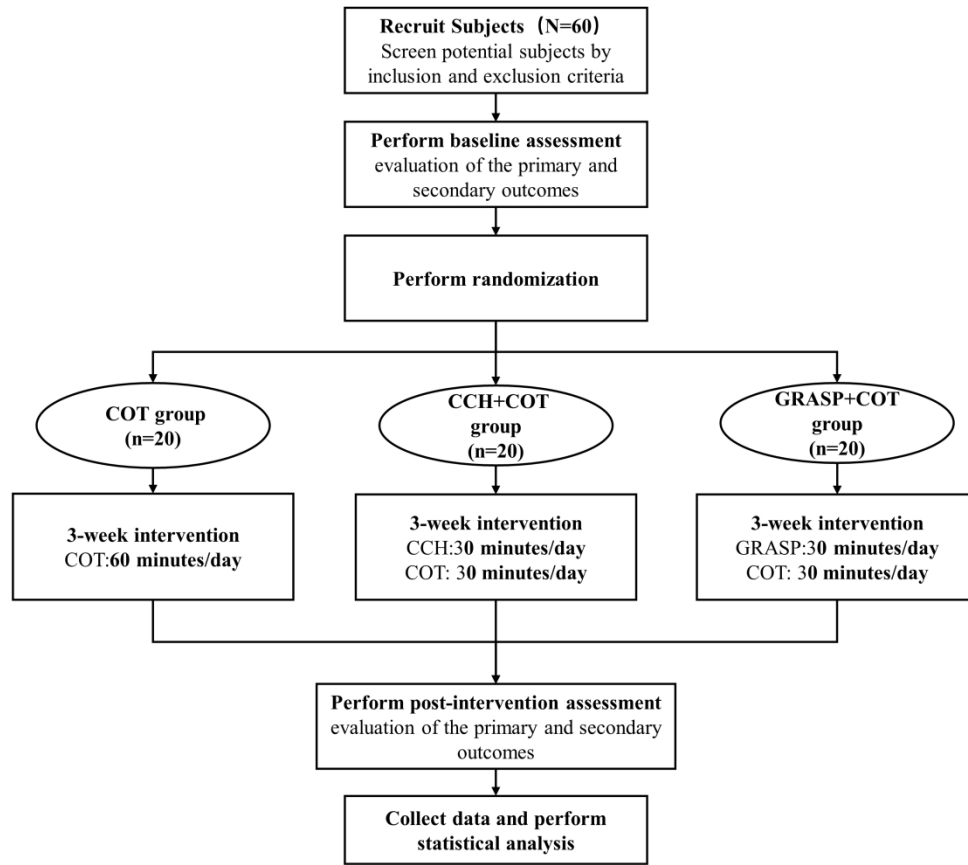
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35 Figure 1. The study flowchart. COT, conventional occupational therapy; CCH, Chinese calligraphy
36 handwriting; GRASP, Graded Repetitive Arm Supplementary Program.

37 240x209mm (300 x 300 DPI)

	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)

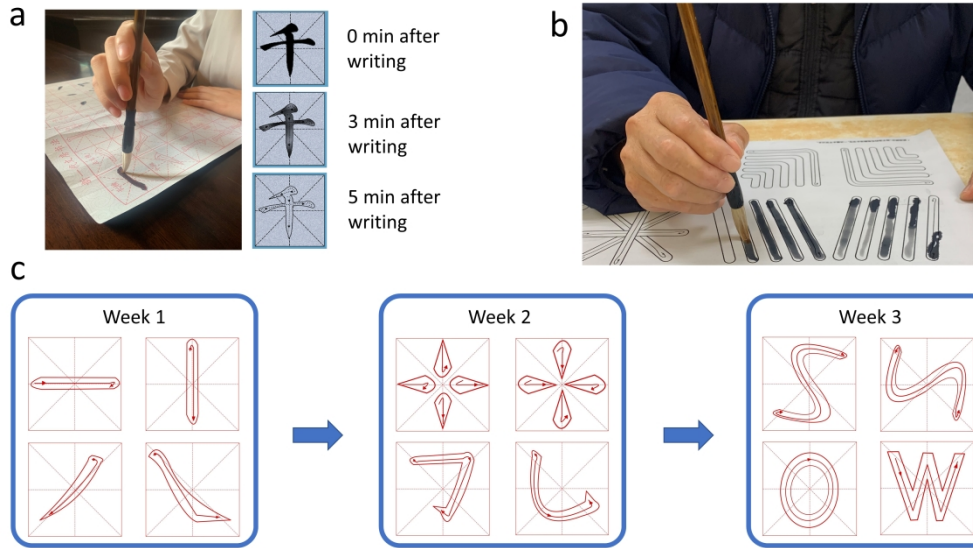


Figure 3. Calligraphy practicing and copybook design. a) Left: standard way of calligraphy handwriting; right: water drying out in 5 mins on the copybook. b) A patient is practicing the calligraphy handwriting. c) The difficulty of calligraphy practicing increases as the character frames become more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

338x190mm (300 x 300 DPI)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	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 ___

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1	Introduction			
2				
3	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
4				
5				
6		6b	Explanation for choice of comparators	5
7				
8	Objectives	7	Specific objectives or hypotheses	5
9				
10	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
11				
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	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
17				
18				
19	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
20				
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
23				
24		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
25				
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
27				
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
29				
30	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
31				
32				
33				
34	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
35				
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1 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_____

2
3
4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____6_____

5
6 **Methods: Assignment of interventions (for controlled trials)**

7
8 Allocation:

9
10 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_____

11
12
13
14 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_____

15
16
17
18 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions _____6_____

19
20 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how _____6_____

21
22
23 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial _____6_____

24
25
26 **Methods: Data collection, management, and analysis**

27
28
29 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_____

30
31
32 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_____

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1	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 _____
2				
3				
4				
5	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 _____
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____ 9 _____
9				
10		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 _____
11				
12				
13				
14	Methods: Monitoring			
15				
16	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 _____
17				
18				
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22		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 _____
23				
24				
25	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 _____
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____ NA _____
29				
30				
31				
32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____ 9 _____
35				
36				
37	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 _____
38				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 10 _____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ 10 _____
5				
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7	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 _____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 10 _____
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 10 _____
14				
15				
16	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 _____
17				
18				
19				
20	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 _____
21				
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23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ 10 _____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ 11 _____
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__Supplementary__
32				
33				
34	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 _____
35				
36				

*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.

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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	伍颢	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			

我们邀请您参与本研究。您参与本研究完全基于自愿原则，您可以拒绝参与或者随时退出实验，不会遭到任何惩罚。

在决定是否参与之前，您需要了解本研究的内容、参与本研究会有哪些风险和益处、以及您在本研究中需要做哪些事情。您也可以与您的家人、朋友或医生共同商讨本研究以及本同意书。如果您对本研究或本同意书有任何疑问，请联系主要研究者和合作研究者。如果您决定参与本研究，必须签署本同意书。我们会提供本同意书的签名副本以供您留存。

1、该研究的目的是什么？

您被邀请参与本研究。本研究的目的是设计并验证一种以中国书法为基础、以恢复中风患者上肢功能为目的的康复治疗，并与目前流行的康复疗法进行比较，从而探讨其对中风患者上肢功能改善的效果。

2、您在该研究中需要做什么？

如果您同意参与该研究，您会被要求进行一项上肢功能康复训练。根据您的分组情况，您将进行书法撰写练习或另一项简单的上肢活动练习（如搭积木、套圈等）。在练习的开始以及结束，您将接受针对您上肢功能、生活活动水平、以及精神健康水平的量表测试。

3、参与该研究需要多长时间？

本研究将持续约3周。您每天练习0.5个小时，每周练习5天，一共7.5小时的康复练习。此外，单次测试环节将持续0.5个小时。

4、可能会有哪些风险或不适？

您可能会产生轻微的上肢疲劳或短暂的局部疼痛等不适反应。

5、参与该研究可能会有哪些益处？

参与本研究将会有助于您中风后的上肢功能恢复。并且本研究将来会使更多的患者受益，因为本研究将会帮助我们更好地了解书法干预对于中风后上肢康复情况的影响。

6、您参与该研究是否会得到报酬？

参与本研究您将免费获得一份上肢功能评估报告和一套书法治疗工具，包括毛笔、字帖和书法教学视频。

7、如果您因参与该研究而受伤怎么办？

您因参与该研究所发生的任何器质性损伤，上海体育学院不会为您支付医疗费用或提供其他经济补偿。您不会因签署本同意书而放弃任何法定权利。

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我已阅读本同意书，我提出的问题均已得到答复。我自愿同意参与本研究，并已收到上述内容的副本。

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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-052046.R1
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Date Submitted by the Author:	11-Jan-2022
Complete List of Authors:	wu, xiaodi; Shanghai University of Sport, ; Zhang, Qiang; Institute for Biomechanics, ETH Zürich, Qiao, Jun; Department of Treatment, The Second Rehabilitation Hospital of Shanghai Chen, Nan; Rehabilitation Department, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine Wu, Xie; Shanghai University of Sport School of Kinesiology,
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	REHABILITATION MEDICINE, Stroke < NEUROLOGY, Neurological injury < NEUROLOGY

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6 1 **A Calligraphy-based Rehabilitation Exercise for Improving the Upper-limb**
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9 2 **Function of Stroke Patients: Protocol for A Randomized Controlled Study**
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35 12 **Article type:** research protocol
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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

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44 **Article summary**

45 **Strengths and limitations of this study**

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

54 Introduction

55 Recent epidemiological studies have revealed that each year near 17 million people suffer from stroke
56 in the world [1-3], and in China alone over 2.5 million new stroke cases are diagnosed per year [3, 4]. With
57 the improved care in the hyperacute and acute periods of stroke, around 80% of stroke patients can survive
58 from the initial injuries [5]. However, stroke can usually lead to severe neuropsychiatric disorders in patients,
59 such as motor capacities, sensory, and cognitive impairments [6, 7]. As one of the most common
60 complications, the motor impairment might affect the unilateral movement abilities of patients' upper limbs
61 [8, 9]. Patients with such upper-limb dysfunctions would exhibit difficulties in contracting muscles, as well
62 as in the control and coordination of their arms, hands, and fingers. The post-stroke upper-limb dysfunctions
63 can thus limit the patients in daily activities such as eating, dressing, and washing [10-12], and increase their
64 dependences and affect the quality of life in a long time period [13]. Therefore, post-stroke rehabilitation of
65 upper-limb dysfunction is critical in restoring patients' upper-limb functions and improving their quality of
66 life [14].

67 By leveraging different technologies, multiple post-stroke rehabilitation therapies have been developed
68 and used to restore upper-limb functions, such as therapist-assisted practice [15-17], bilateral training [18],
69 constraint-induced movement therapy (CIMT) [19], robotic-assisted therapy [20], mirror therapy [21], and
70 virtual reality [22]. As the function recovery can last into the chronic phase of stroke [23], there is an
71 increasing interest in validating interventions that aim to enhance the physical and psychological well-being
72 in both acute and chronic periods of post-stroke rehabilitation. It is recognized that therapies involving high-
73 intensity repetitive tasks, such as the CIMT, have the best effect on the recovery of upper-limb functions
74 [8]. However, by limiting the contralateral arm the CIMT forces the patient to use the impaired arm, and
75 thus challenges the patient's compliance during therapy [19, 24] so that treatment outcomes are
76 compromised [25, 26]. Therefore, high-intensity repetitive therapies might not be optimal for long-term
77 rehabilitation of post-stroke upper-limb dysfunctions as well as for the improvement of the psychological
78 well-being of the patients. The therapies supervised by therapists or with sophisticated equipment can
79 increase the financial pressure of the patients [27, 28], and thus might not be widely accepted for long-term
80 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

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4 109 other exercises. Calligraphy copybook is prevalently used at the beginning of CCH self-practicing because
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6 110 the character frames in the copybook can regulate people's writing styles without the need of instructors.
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8 111 Thus, the calligraphy copybook may be an excellent tool for stroke patients to practice the CCH exercise at
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10 112 both hospital and home. In addition to Chinese characters, the copybook can also be designed by including
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12 113 characters of other languages to make it more suitable for patients with other cultural backgrounds.
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14 114 Therefore, the purpose of this study is to develop a CCH-based interventive exercise with a self-designed
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16 115 calligraphy copybook and validate its effect on the improvement of patients' upper-limb functions in the
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119 **Methods**

120 **Study design**

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

129 [Insert Fig. 1 here]

130 [Insert Fig. 2 here]

131 **Subject recruitment and randomization**

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

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

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4 145 #2 (COT+CCH group), or #3 (COT+GRASP group) [38]. Once a patient is recruited, the authors will open
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6 146 an envelope sequentially and allocate the patient into a group according to the internal group number. The
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8 147 external series number on the envelope will also be used as the ID of each patient to track their information
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10 148 and data throughout the entire study, which makes the assessor blind to the group allocation.

12 149 **Sample size**

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15 150 According to a previous study [39], the minimal clinical important difference for the Action Research
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17 151 Arm Test scale is 6 in patients with chronic stroke. The mean score that patients with chronic stroke can
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19 152 achieve was reported to be about 30 [40]. Thus, the effect size is estimated to be 0.2. The sample size was
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21 153 then calculated using this value in G*Power 3 (Erdfelder, Faul, & Buchner, 1996). To achieve a power of
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23 154 80% ($\alpha = 0.05$), a minimum of 18 subjects is required for each group. Taking this rate into consideration,
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25 155 a total of 60 patients (20 per group) will be recruited in the study.

27 156 **Interventions**

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30 157 All patients will receive rehabilitation interventions based on routine treatment and daily nursing in the
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32 158 hospital. The rehabilitation interventions will be carried out 5 days per week for a total of 3 weeks.

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35 159 In the COT group, the patients will receive 60-mins COT treatment five times per week. The treatment
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37 160 will be performed by a therapist, which comprises task-related practices for gross movements and dexterity,
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39 161 including different grips, selective finger movements, strength training, stretching, and daily life activities.

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41 162 In the COT+CCH group, the patients will receive 30-mins COT treatment and 30-mins CCH training
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43 163 five times per week. The CCH training will be performed on self-designed copybooks with hollowed-out
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45 164 character frames (Fig. 3a). The copybooks are reusable as the water dries out in 5 minutes. During writing,
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47 165 the patients will be required to sit in front of a desk. The patients hold a calligraphy brush using the thumb,
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49 166 index finger, and middle finger of the affected hand, soak its head with water, and then fill the character
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51 167 frames on the copybook (Fig. 3b). Three different copybooks with increasing difficulties are designed, and
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53 168 each will be used in the CCH training for 1 week (Fig. 3c). This design can enable the patients to imitate
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55 169 geometric shapes, beginning with straight lines, followed by more complicated circles and curves, which
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57 170 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.
- Gripping 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

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4 197 pick up pins one at a time and place them in a row of holes.
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- 6 198
- 7 198 • Disabilities of arm, shoulder, and hand (DASH) [48]: This measure is a 30-item self-report
8 199 questionnaire, which is designed to assess individually rated upper limb impairments and
9 199 impacts on activities for patients with musculoskeletal conditions in the upper limbs.
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 - 11 200 • Quality of life (short form 36, SF-36) [49]: This measure is a generic self-report of health status
12 201 for evaluating the quality of life that relates to physical and mental well-being.
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17 203 **Statistical method**

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20 204 Two-way analysis of variance (ANOVA) will be applied to examine the interaction and the main effects
21 of the intervention method and the assessment time. The effects of the intervention will be analyzed by
22 205 comparing the changes in the functionality of the affected upper extremity between groups using the analysis
23 of covariance of change score, with the baseline as covariate and by adjusting for possible confounders. If
24 206 significant interaction is found, Tukey *post hoc* tests will be performed. Demographic characteristics and
25 other baseline values will be described using descriptive statistics for each group. Significant level for all
26 207 tests will be set at $P < 0.05$ for all statistical tests and corrected for multiple comparisons using the Bonferroni
27 method. All statistical analysis will be performed using SPSS (version 13.0; SPSS Inc., Chicago, IL, USA).
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38 213 During patient recruitment, 3 senior neurologists will jointly evaluate each patient's stroke status based
39 on his medical record. The experimental data will be reviewed and verified by a senior researcher.
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42 43 215 **Management of adverse events**

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45 216 Possible adverse events include shoulder pain, hand soreness and numbness, and muscle fatigue. The
46 patients will be instructed to rate and report the severity of pain and fatigue from 0 (e.g., no pain) to 10 (e.g.,
47 217 unbearable pain) at the end of each treatment. The research team will record the adverse event, including
48 duration, severity, and position. If any patient reports severe adverse events that may affect the progressing
49 218 of the intervention, the test will be paused, and relieving treatment will be provided. If the symptom cannot
50 be relieved, the intervention will be terminated.
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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

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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.

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4 258 **Author statement**
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7 259 Xiaodi Wu: Perform the preliminary experiment; write the manuscript
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10 260 Qiang Zhang: Design the experiment; write the manuscript (joined); edit the manuscript
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12 261 Jun Qiao: Perform the preliminary experiment
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15 262 Nan Chen: Supervise the experiment
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17 263 Xie Wu: Design the experiment, be the PI of the project
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265 **Titles of figures**

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

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

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

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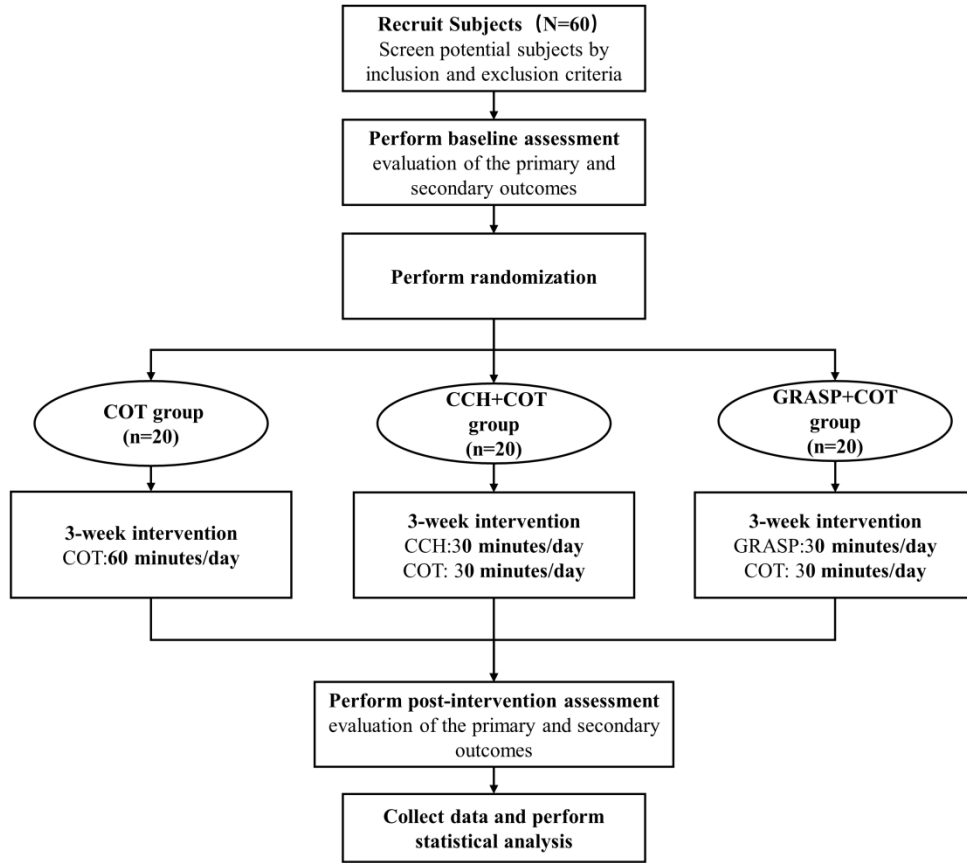


Figure 1. The study flowchart. COT, conventional occupational therapy; CCH, Chinese calligraphy handwriting; GRASP, Graded Repetitive Arm Supplementary Program.

240x209mm (300 x 300 DPI)

	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)

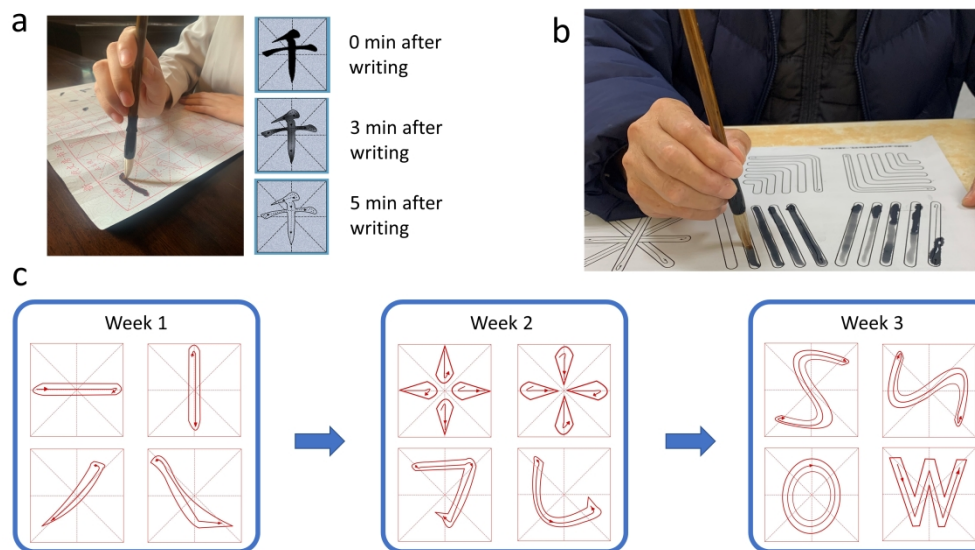


Figure 3. Calligraphy practicing and copybook design. a) Left: standard way of calligraphy handwriting; right: water drying out in 5 mins on the copybook. b) A patient is practicing the calligraphy handwriting. c) The difficulty of calligraphy practicing increases as the character frames become more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

338x190mm (300 x 300 DPI)

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3 Supplementary of:
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5 **A Calligraphy-based Rehabilitation Exercise for Improving the Upper-limb Function of Stroke**
6 **Patients: Protocol for A Randomized Controlled Study**
7

8
9 *Xiaodi Wu**, *Qiang Zhang**, *Jun Qiao*, *Nan Chen[#]*, *Xie Wu[#]*
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13 Below describes the details of the rating scales that will be used in the experiment:
14

15
16 1) Primary outcome measures
17

- 18 • Action Research Arm Test (ARAT): The ARAT was developed by Lyle in 1981 to measure
19 function of the arm and hand in a variety of tasks, with special focus on fine motor function
20 of hands. all 19 items of the ARAT are scored on a 4-point scale (0-3). Scores are judged as
21 follows. 0, the patient is unable to perform any part of the task; 1, the patient is able to
22 completely lift the object from the flat platform; 2, the function is completely completed but
23 is very clumsy or very difficult; and 3, the movement is completed normally. The scores for
24 each item were calculated by summing the total score for each side, ranging from 0 to 57
25 [1]. In addition, the overall time for patient to complete the ARAT will be recorded. The
26 ARAT has good predictive and concurrent validity [2].
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33 2) Secondary outcome measures
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- 35 • Fugl-Meyer assessment-UE (FMA-UE): The FMA was designed in 1975 as a global
36 assessment index for quantitative assessment of recovery of post-stroke paraplegic limbs. It
37 is a quantitative performance-based measure consisting of 33 items that measure motor
38 function of the upper limb. Each item is scored on a 3-point scale (0=can't perform, 1=can
39 partially perform, 2=can fully perform), and the maximum score is 66. The severe degree
40 of paresis was distributed according to the FMA score as follows. ≤25 points: severe, 26 to
41 45 points: moderate, and 46 to 66 points: mild [3]. The FMA has a high inter-rater and test-
42 retest reliability [4].
43
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47 • Gripping strength of the affected hand: The grip force of the affected hand was measured
48 with a dynamometer (Xiangshan, EH-101). The patient insisted the gripping at his/her best
49 for three seconds, and then rested for 30 s. The test was performed three times, and the
50 maximum value was recorded.
51
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53
54 • Purdue pegboard (PPB): The PPB was developed by Tiffin in 1948 to measure gross motor
55 skill in the use of the arm, hand, and fingers, as well as fingertip dexterity. It consists of five
56 subtests: dominant hand (D), non-dominant hand (ND), both hands (B), dominant +non-
57 dominant+ both hands (D+ND+B), and an assembly subtest. In the five subtests, very small
58 pins, washers, and collars were manipulated with one and two hands, and participants were
59
60

1
2
3 asked to place as many pins as possible into the holes within 30 seconds. In subtests D, ND,
4 and B, the number of pins placed within 30 s was recorded. scores for subtests D+ND+B
5 could be calculated from the scores of the first three tests. The assembly subtest score is the
6 total number of pins, washers, and collars placed in 60 s [5]. PPB has good predictive and
7 concurrent validity [6].
8
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- 10
11 • Disabilities of arm, shoulder, and hand (DASH) : DASH is a 30-item self-report
12 questionnaire designed to assess individual ratings of upper limb impairment and effects on
13 activity in patients with upper limb musculoskeletal disorders. The items ask about the level
14 of difficulty in performing different physical activities due to upper limb problems (21
15 items), the severity of symptoms such as upper limb pain, weakness and stiffness (5 items),
16 and the impact of the problem on social activity participation, etc. (4 items). Each item has
17 five options for response, with scores ranging from 0 (no disability) to 100 (most severe
18 disability), with higher scores indicating greater disability. DASH has good internal
19 consistency and validity in adults following stroke [7].
20
21
- 22 • Quality of life (short form 36, SF-36) : SF-36 was normalized in 1990 as a self-report
23 measure of functional health and well-being. The SF-36 consists of eight health scales.
24 Physical Functioning (10 items), Role Limitation-Physical (4 items), Physical Pain (2 items),
25 General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role Limitation-
26 Emotional (3 items), and Mental Health (5 items). A score from 0 (the worst health measure)
27 to 100 (the best health measure) was calculated for each scale. SF-36 has good internal
28 consistencies and group differences validity in stroke patients [8, 9].
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	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 ___

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1	Introduction			
2				
3	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
4				
5				
6		6b	Explanation for choice of comparators	5
7				
8	Objectives	7	Specific objectives or hypotheses	5
9				
10	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
11				
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	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
17				
18				
19	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
20				
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
23				
24		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
25				
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
27				
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
29				
30	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
31				
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34	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
35				
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1	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_____
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3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____6_____
5				
6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	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_____
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16	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_____
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____6_____
21				
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____6_____
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____6_____
28				
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30				
31	Methods: Data collection, management, and analysis			
32				
33	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_____
34				
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39		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_____
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1	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 _____
2				
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5	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 _____
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7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____ 9 _____
9				
10		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 _____
11				
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13				
14	Methods: Monitoring			
15				
16	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 _____
17				
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22		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 _____
23				
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25	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 _____
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____ NA _____
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____ 9 _____
35				
36				
37	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 _____
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 10 _____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ 10 _____
5				
6				
7	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 _____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 10 _____
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 10 _____
14				
15				
16	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 _____
17				
18				
19				
20	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 _____
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ 10 _____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ 11 _____
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__Supplementary__
32				
33				
34	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 _____
35				
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*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.

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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-052046.R2
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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	REHABILITATION MEDICINE, Stroke < NEUROLOGY, Neurological injury < NEUROLOGY

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6 1 **A Calligraphy-based Rehabilitation Exercise for Improving the Upper-limb**
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9 2 **Function of Stroke Patients: Protocol for an Evaluator-blinded Randomized**
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12 3 **Controlled Trial**
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33 11 *#These authors have contributed equally to this work and share corresponding authorship*
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38 13 **Article type:** research protocol

39
40 14 **Funding:** Special Health Research Project of Shanghai Municipal Health Commission on the Health of
41
42 15 Aging, Woman and Children (2020YJZX0137)

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45 16 **Author declaration:** The authors have declared no conflict of interest

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47 17 **Word count:** 2508

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For peer review only

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.

58 Introduction

59 Recent epidemiological studies have revealed that each year near 17 million people suffer from stroke
60 in the world [1-3], and in China alone over 2.5 million new stroke cases are diagnosed per year [3, 4]. With
61 the improved care in the hyperacute and acute periods of stroke, around 80% of stroke patients can survive
62 from the initial injuries [5]. However, stroke can usually lead to severe neuropsychiatric disorders in patients,
63 such as motion capacities, sensory, and cognitive impairments [6, 7]. As one of the most common
64 complications, the motor impairment might affect the unilateral movement abilities of patients' upper limbs
65 [8, 9]. Patients with such upper-limb dysfunctions would exhibit difficulties in contracting muscles, as well
66 as in the control and coordination of their arms, hands, and fingers. The post-stroke upper-limb dysfunctions
67 can thus limit the patients in daily activities such as eating, dressing, and washing [10-12], and increase their
68 dependences and affect the quality of life in a long time period [13]. Therefore, post-stroke rehabilitation of
69 upper-limb dysfunction is critical in restoring patients' upper-limb functions and improving their quality of
70 life [14].

71 By leveraging different technologies, multiple post-stroke rehabilitation therapies have been developed
72 and used to restore upper-limb functions, such as therapist-assisted practice [15-17], bilateral training [18],
73 constraint-induced movement therapy (CIMT) [19], robotic-assisted therapy [20], mirror therapy [21], and
74 virtual reality [22]. As the function recovery can last into the chronic phase of stroke [23], there is an
75 increasing interest in validating interventions that aim to enhance the physical and psychological well-being
76 in both acute and chronic periods of post-stroke rehabilitation. It is recognized that therapies involving high-
77 intensity repetitive tasks, such as the CIMT, have the best effect on the recovery of upper-limb functions
78 [8]. However, by limiting the contralateral arm the CIMT forces the patient to use the impaired arm, and
79 thus challenges the patient's compliance during therapy [19, 24] so that treatment outcomes are
80 compromised [25, 26]. Therefore, high-intensity repetitive therapies might not be optimal for long-term
81 rehabilitation of post-stroke upper-limb dysfunctions as well as for the improvement of the psychological
82 well-being of the patients. The therapies supervised by therapists or with sophisticated equipment can
83 increase the financial pressure of the patients [27, 28], and thus might not be widely accepted for long-term
84 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

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

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123 **Methods**

124 **Study design**

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

133 [Insert Fig. 1 here]

134 [Insert Fig. 2 here]

135 **Subject recruitment and randomization**

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

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

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4 149 #2 (COT+CCH group), or #3 (COT+GRASP group) [38]. Once a patient is recruited, the authors will open
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6 150 an envelope sequentially and allocate the patient into a group according to the internal group number. The
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8 151 external series number on the envelope will also be used as the ID of each patient to track their information
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10 152 and data throughout the entire study, which makes the assessor blind to the group allocation.

12 153 **Sample size**

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15 154 According to a previous study [39], the minimal clinical important difference for the Action Research
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17 155 Arm Test scale is 6 in patients with chronic stroke. The mean score that patients with chronic stroke can
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19 156 achieve was reported to be about 30 [40]. Thus, the effect size is estimated to be 0.2. The sample size was
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21 157 then calculated using this value in G*Power 3 (Erdfelder, Faul, & Buchner, 1996). To achieve a power of
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23 158 80% ($\alpha = 0.05$), a minimum of 18 subjects is required for each group. Taking this rate into consideration,
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25 159 a total of 60 patients (20 per group) will be recruited in the study.

28 160 **Interventions**

30 161 All patients will receive rehabilitation interventions based on routine treatment and daily nursing in the
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32 162 hospital. The rehabilitation interventions will be carried out 5 days per week for a total of 3 weeks.

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35 163 In the COT group, the patients will receive 60-mins COT treatment five times per week. The treatment
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37 164 will be performed by a therapist, which comprises task-related practices for gross movements and dexterity,
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39 165 including different grips, selective finger movements, strength training, stretching, and daily life activities.

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41 166 In the COT+CCH group, the patients will receive 30-mins COT treatment and 30-mins CCH training
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43 167 five times per week. The CCH training will be performed on self-designed copybooks with hollowed-out
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45 168 character frames (Fig. 3a). The copybooks are reusable as the water dries out in 5 minutes. During writing,
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47 169 the patients will be required to sit in front of a desk. The patients hold a calligraphy brush using the thumb,
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49 170 index finger, and middle finger of the affected hand, soak its head with water, and then fill the character
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51 171 frames on the copybook (Fig. 3b). Three different copybooks with increasing difficulties are designed, and
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53 172 each will be used in the CCH training for 1 week (Fig. 3c). This design can enable the patients to imitate
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55 173 geometric shapes, beginning with straight lines, followed by more complicated circles and curves, which
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57 174 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.
- Gripping 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

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4 227 be relieved, the intervention will be terminated.
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6 228 **Patient and public involvement**

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9 229 The initial research idea was conceived by the authors and modified according to face-to-face
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11 230 interviews with stroke patients and their guardians. Before the formal experiment, 5 stroke patients will be
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13 231 invited to practice the CCH and GRASP. The intervention protocols will be adjusted based on their feedback
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15 232 to ensure the safety and applicability of the intervention. The potential risks and benefits of the study will
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17 233 be fully explained to the patients and their guardians before signing the informed consent, and the study
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19 234 results will be released to them on request.
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21 235 **Ethics and dissemination**

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24 236 This study will be conducted in accordance with the principles of the Declaration of Helsinki. The
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26 237 ethics approvals have been obtained from the Research Ethics Committee of the Second Rehabilitation
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28 238 Hospital of Shanghai (Study ID: 2020-32-01, approved date: December 15, 2020) and the Shanghai
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30 239 University of Sport (Study ID: 102772021RT043, approved date: January 19, 2021). The authors will
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32 240 communicate the study information, including the study aims, the recruitment criteria, the study protocols,
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34 241 the potential risks, and the expected outcomes to the recruited patients. The authors will provide direct
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36 242 consultation to all patients and their guardians to address any concerns they may encounter. The patients
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38 243 and their guardians will make the final decision to join or withdraw from the study. All the recruited patients
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40 244 will sign the informed consent before the study.
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42 245 Patients' identifiable information will be stored separately from their clinical information and research
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44 246 data by one of the authors who is in charge of the patient randomization. In order to protect patients'
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46 247 confidentiality, only the director of the study, this author, and the ethics committee will have access to the
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48 248 patients' personal information and medical records. At the end of the study, the data will be saved on a
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50 249 password-protected hard drive, and will be discarded 3 years after the study.
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52 250 The results of the study will be published in peer-reviewed scientific journals and presented at
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54 251 conferences and workshops within 12 months after study completion. According to the instructions of the
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56 252 International Committee of Medical Journal Editors, individuals who meet the criteria for authorship will
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58 253 be included as authors of the publications. The CCH exercise and the corresponding equipment (copybook,
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calligraphy brush, etc.) will be optimized and promoted to the vast physiotherapists to enable the clinical transition.

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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.

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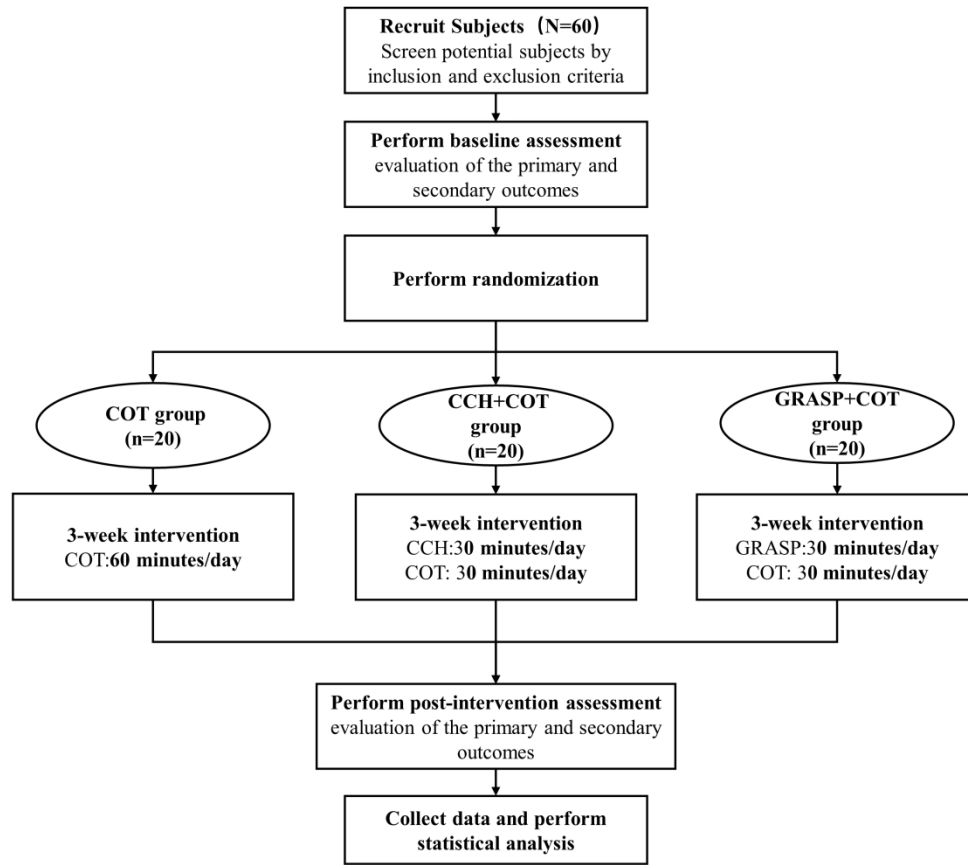
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35 Figure 1. The study flowchart. COT, conventional occupational therapy; CCH, Chinese calligraphy
36 handwriting; GRASP, Graded Repetitive Arm Supplementary Program.

37 240x209mm (300 x 300 DPI)

	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)

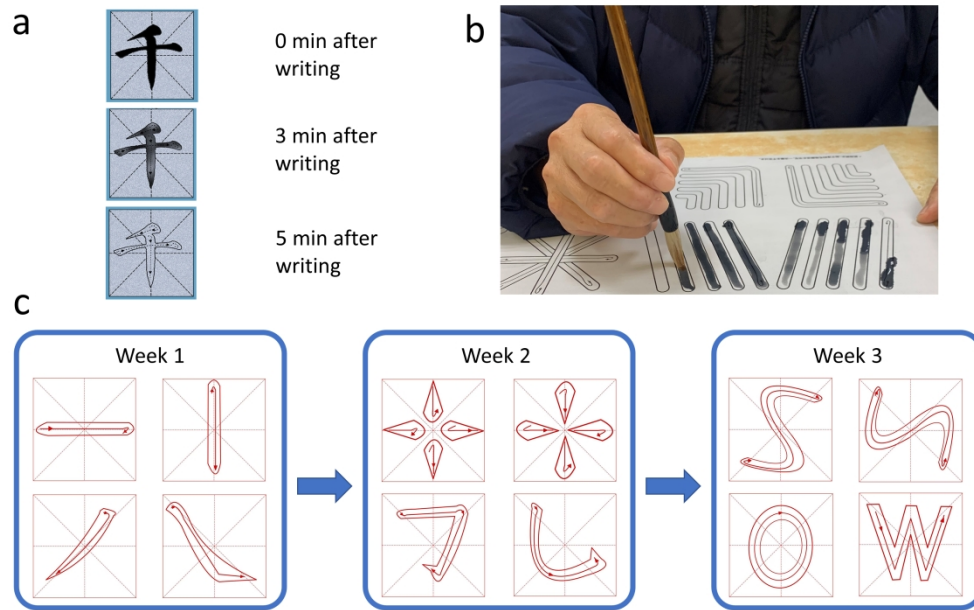


Figure 3. Calligraphy practicing and copybook design. a) Water drying out in 5 mins on the copybook. b) A patient is practicing the calligraphy handwriting. c) The difficulty of calligraphy practicing increases as the character frames become more complicated.

307x190mm (300 x 300 DPI)

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3 Supplementary of:
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5 **A Calligraphy-based Rehabilitation Exercise for Improving the Upper-limb Function of Stroke**
6 **Patients: Protocol for A Randomized Controlled Study**
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8
9 *Xiaodi Wu**, *Qiang Zhang**, *Jun Qiao*, *Nan Chen[#]*, *Xie Wu[#]*
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13 Below describes the details of the rating scales that will be used in the experiment:
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15
16 1) Primary outcome measures
17

- 18 • Action Research Arm Test (ARAT): The ARAT was developed by Lyle in 1981 to measure
19 function of the arm and hand in a variety of tasks, with special focus on fine motor function
20 of hands. all 19 items of the ARAT are scored on a 4-point scale (0-3). Scores are judged as
21 follows. 0, the patient is unable to perform any part of the task; 1, the patient is able to
22 completely lift the object from the flat platform; 2, the function is completely completed but
23 is very clumsy or very difficult; and 3, the movement is completed normally. The scores for
24 each item were calculated by summing the total score for each side, ranging from 0 to 57
25 [1]. In addition, the overall time for patient to complete the ARAT will be recorded. The
26 ARAT has good predictive and concurrent validity [2].
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33 2) Secondary outcome measures
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- 35 • Fugl-Meyer assessment-UE (FMA-UE): The FMA was designed in 1975 as a global
36 assessment index for quantitative assessment of recovery of post-stroke paraplegic limbs. It
37 is a quantitative performance-based measure consisting of 33 items that measure motor
38 function of the upper limb. Each item is scored on a 3-point scale (0=can't perform, 1=can
39 partially perform, 2=can fully perform), and the maximum score is 66. The severe degree
40 of paresis was distributed according to the FMA score as follows. ≤25 points: severe, 26 to
41 45 points: moderate, and 46 to 66 points: mild [3]. The FMA has a high inter-rater and test-
42 retest reliability [4].
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47 • Gripping strength of the affected hand: The grip force of the affected hand was measured
48 with a dynamometer (Xiangshan, EH-101). The patient insisted the gripping at his/her best
49 for three seconds, and then rested for 30 s. The test was performed three times, and the
50 maximum value was recorded.
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54 • Purdue pegboard (PPB): The PPB was developed by Tiffin in 1948 to measure gross motor
55 skill in the use of the arm, hand, and fingers, as well as fingertip dexterity. It consists of five
56 subtests: dominant hand (D), non-dominant hand (ND), both hands (B), dominant +non-
57 dominant+ both hands (D+ND+B), and an assembly subtest. In the five subtests, very small
58 pins, washers, and collars were manipulated with one and two hands, and participants were
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1
2
3 asked to place as many pins as possible into the holes within 30 seconds. In subtests D, ND,
4 and B, the number of pins placed within 30 s was recorded. scores for subtests D+ND+B
5 could be calculated from the scores of the first three tests. The assembly subtest score is the
6 total number of pins, washers, and collars placed in 60 s [5]. PPB has good predictive and
7 concurrent validity [6].
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- 10
11 • Disabilities of arm, shoulder, and hand (DASH) : DASH is a 30-item self-report
12 questionnaire designed to assess individual ratings of upper limb impairment and effects on
13 activity in patients with upper limb musculoskeletal disorders. The items ask about the level
14 of difficulty in performing different physical activities due to upper limb problems (21
15 items), the severity of symptoms such as upper limb pain, weakness and stiffness (5 items),
16 and the impact of the problem on social activity participation, etc. (4 items). Each item has
17 five options for response, with scores ranging from 0 (no disability) to 100 (most severe
18 disability), with higher scores indicating greater disability. DASH has good internal
19 consistency and validity in adults following stroke [7].
20
21
- 22 • Quality of life (short form 36, SF-36) : SF-36 was normalized in 1990 as a self-report
23 measure of functional health and well-being. The SF-36 consists of eight health scales.
24 Physical Functioning (10 items), Role Limitation-Physical (4 items), Physical Pain (2 items),
25 General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role Limitation-
26 Emotional (3 items), and Mental Health (5 items). A score from 0 (the worst health measure)
27 to 100 (the best health measure) was calculated for each scale. SF-36 has good internal
28 consistencies and group differences validity in stroke patients [8, 9].
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	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 ___

1 Introduction

2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	4
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	5
7				
8	Objectives	7	Specific objectives or hypotheses	5
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	6
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	6
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	7
23			administered	
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	7
25			change in response to harms, participant request, or improving/worsening disease)	
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	7
27			(eg, drug tablet return, laboratory tests)	
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	8
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
32			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
33			efficacy and harm outcomes is strongly recommended	
34				
35	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	7
36			participants. A schematic diagram is highly recommended (see Figure)	
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1	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_____
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____6_____
5				
6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	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_____
11				
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16	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_____
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____6_____
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____6_____
25				
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____6_____
28				
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31	Methods: Data collection, management, and analysis			
32				
33	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_____
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39		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_____
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1	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 _____
2				
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5	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 _____
6				
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____ 9 _____
9				
10		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 _____
11				
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14	Methods: Monitoring			
15				
16	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 _____
17				
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22		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 _____
23				
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25	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 _____
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____ NA _____
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____ 9 _____
35				
36				
37	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 _____
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 10 _____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ 10 _____
5				
6				
7	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 _____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 10 _____
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 10 _____
14				
15				
16	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 _____
17				
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19				
20	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 _____
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ 10 _____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ 11 _____
27				
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29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__Supplementary__
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34	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 _____
35				
36				

37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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