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Effect of Baduanjin exercise on cognitive function in patients with post-stroke cognitive impairment: Study protocol for a randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020954
Article Type:	Protocol
Date Submitted by the Author:	06-Dec-2017
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Keywords:	Baduanjin exercise, cognitive impairment after stroke, randomized controlled trial

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3 **Effect of Baduanjin exercise on cognitive function in patients with**
4 **post-stroke cognitive impairment: Study protocol for a randomized**
5 **controlled trial**
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16
17
18 **Abstract**

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20 **Introduction:** Post-stroke cognitive impairment is one of the most common
21 complications in stroke survivors, and over 65% of these patients suffer from
22 cognitive impairment at 12 months following onset, which strongly affects the
23 rehabilitation of their motor function and quality of life. Therefore, it is important to
24 improve the cognitive ability of stroke survivors. As an important component of
25 traditional Chinese Qigong exercises, characterized by the coordination of mind and
26 body with a low exercise intensity, Baduanjin has the potential benefit of improving
27 cognitive ability for stroke patients with cognitive impairment. The primary purpose
28 of this study is to investigate the effectiveness and safety of Baduanjin training on the
29 cognitive function of stroke survivors.
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43 **Method and analysis:** This study is designed as a randomized, two-arm parallel
44 controlled trial with allocation concealment and assessors blinding. A total of 48
45 participants will be recruited and randomly allocated into the Baduanjin exercise
46 intervention or control group. Baduanjin intervention will last 24 weeks with a
47 frequency of 3 days a week and 40 min a day. Global cognitive function and the
48 specific domains of cognition (i.e., memory, processing speed, execution, attention
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3 and visuospatial ability) will be measured at baseline, 8 weeks, 16 weeks, 24 weeks
4 after intervention and 28 weeks after an additional 4-week follow-up period, while the
5 motor function and quality of life will be measured at baseline, 24 weeks after
6 intervention, and 28 weeks after an additional 4-week follow-up period.
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12 **Discussion:** This protocol presents a rigorous design of a randomized parallel
13 controlled trial that aims to evaluate the effectiveness of Baduanjin exercise on
14 cognitive function, motor function and quality of life in stroke patients with cognitive
15 impairment. A positive result will provide powerful evidence for Baduanjin exercise
16 to improve cognitive function, motor function and quality of life in stroke survivors
17 with cognitive impairment.
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26 **Ethics and dissemination:** Ethics approval was obtained from the Ethics Committee
27 of Fujian University of Traditional Chinese Medicine Subsidiary Rehabilitation
28 Hospital (approval number: 2016KY-022-01). The findings will be disseminated
29 through peer-reviewed publications and at scientific conferences.
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35 **Strengths and limitations of this study**

- 36 ● This protocol presents a rigorous design of a randomized parallel controlled trial
37 that aims to evaluate the effectiveness of Baduanjin exercise on the cognitive
38 function, motor function and quality of life in stroke patients with cognitive
39 impairment.
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- 46 ● A broad measurement tool and multiple measurement time points will be used to
47 judge the effects of Baduanjin exercise on cognitive ability in stroke patients.
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- 51 ● If the result we will reach is positive, that will provide a powerful evidence of
52 Baduanjin exercise on improve cognitive function, motor function and quality of
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3 life in stroke survivors with cognitive impairment.

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5 ● The efficacy of a 24-week Baduanjin exercise intervention in stroke patients with
6
7 cognitive impairment remains to be determined.
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10 **Trial registration**

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13 ChiCTR-INR-16009364. Registration date: 10 October, 2016.
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15

16 **Protocol version:** 3.0. Date: 10 October, 2016.
17

18 **Keywords**

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21 Baduanjin exercise, cognitive impairment after stroke, randomized controlled trial
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33 **Background**

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35 Stroke affects 15 million people annually and is a leading cause of death and
36 disability worldwide ^[1]. In China, there are 6 million patients suffering from stroke,
37 and this number increases at an annual rate of 9%. Stroke is associated with many
38 long-term complications, such as motor dysfunction, language dysfunction and
39 cognitive impairment. Post-stroke cognitive impairment is one of most common
40 complications. Over 65% of stroke survivors suffer from cognitive impairment at 12
41 months following onset, and a third of them may transform to dementia ^[2], which
42 greatly impacts the quality of life of stroke survivors ^[3]. As a consequence, it is
43 significant to improve the cognitive function as soon as possible to promote functional
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3 recovery and improve quality of life in stroke survivors [4].
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6 Theoretically, pharmacological therapy for cognition function may lead to
7 improved recovery. Current data also indicate that a number of drugs may have
8 short-term benefits [5-7], but no drug treatment to date has shown convincing clinical
9 evidence on preventing further cognitive decline or restoring cognitive function for
10 stroke survivors [8]. Thus, increasing attention has been paid to non-drug treatments.
11
12 Aerobic exercises have been widely recognized because of their obvious effect of
13 improving cognitive ability in stroke survivors [9-11]. However, most stroke patients do
14 not have sufficient compliance to achieve sufficient improvements in aerobic exercise
15 protocols due to an important concern of safety. Therefore, future stroke studies
16 involving aerobic exercise training should determine optimal protocols for individuals
17 with physical limitations [12]. As a mind-body exercise with mild to moderate intensity,
18 Baduanjin exercise is one of the most common forms of Qigong that has been
19 practised in China for more than 1000 years [13]. Baduanjin exercise consists of eight
20 separate and smooth movements and is easier to learn and practice with less limitation
21 than other aerobic exercises [14]. Therefore, this exercise is more suitable for older
22 adults, especially stroke patients. Increasing studies have demonstrated that regular
23 practice of Baduanjin exercise was beneficial to improve the physical and
24 psychological outcomes in older people, such as improving blood lipid metabolism
25 and sleep quality, lowering blood pressure, reducing depression and anxiety, and
26 improving physical flexibility [15-19]. Currently, several studies also show that regular
27 Baduanjin exercise could slow normal age-related decline in the memory domain, and
28 delay ageing of intelligence in older adults [20-21]. Consequently, we speculate that
29 regular Baduanjin exercise could be beneficial for cognitive function in patients with
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3 post-stroke cognitive dysfunction. The primary aim of this study is to conduct a
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5 randomized controlled trial to evaluate systematically the effect of Baduanjin exercise
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7 on the cognitive function in stroke patients with cognitive impairment.
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10 **Method/Design**

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13 This report describes a two-arm, randomized, parallel controlled trial with allocation
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15 concealment and assessor blinding. The primary purpose is to evaluate the effect of
16
17 Baduanjin on cognitive functions, including global cognitive ability, and primary
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19 cognitive domains, such as memory, attention, and visuospatial ability, in stroke
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21 patients with cognitive impairment.
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25 This study will be conducted at the Wufeng Community Centre in the Gulou
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27 District and the Cangxia Community Centre in the Taijiang District, Fuzhou City,
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29 Fujian, China, which are counterpart support communities of the Affiliated
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31 Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine. A total
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33 of 48 eligible participants will be randomly allocated to either the intervention group
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35 (the Baduanjin exercise group) or the control group (the health education group) in a
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37 1:1 ratio. The participants in the intervention group will accept Baduanjin exercise
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39 training intervention three times a week and the routine health education once every
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41 four weeks for 24 weeks, while those allocated to the control group will only receive
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43 the routine health education once every four weeks for 24 weeks. Primary and
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45 secondary outcomes will be measured at baseline, 8 weeks, 16 weeks and 24 weeks
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47 after intervention and at 28 weeks (after an additional 4-week follow-up period). A
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49 flow diagram of the study design is shown in Figure 1. The study protocol is reported
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51 according to Standard Protocol Items: Recommendations for Intervention Trials 2013
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53 (SPIRIT). A SPIRIT Checklist and the schedule of enrolment, interventions and
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assessments are provided in Additional file 1 and Figure 2.

Sample size

Sample size was calculated on the basis of the changes in global cognitive ability after 24 weeks of intervention between comparison groups with a significance level of 5% and a two-tailed critical region. The means and their standard deviations (mean \pm SD) of global cognitive ability in the control and aerobic exercise intervention group were 75.93 \pm 4.9 and 81.07 \pm 6.16, respectively, at post-intervention according to the published literature [22]. A sample size of 40 participants was calculated to ensure the same effect size with 80% power by Gpower 3.1.9.2 software. Considering a 20% attrition rate, a total of 48 participants is necessary, with 24 participants being assigned to each group.

Study population

The study population is stroke patients with a diagnosis of cognitive impairment living in Fuzhou City. The inclusion and exclusion criteria for the study sample are as follows.

Inclusion criteria

The eligible participants should meet all of the following criteria:

- ① Clinical diagnosis of stroke according to the fourth national academic conference on cerebrovascular diseases Diagnostic Criteria for All Kinds of Cerebrovascular Disease [23] and confirmed by computed tomography or magnetic resonance imaging;
- ② Have cognitive impairment diagnosed by Diagnostic and Statistical Manual Disorders (DSM-V);

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3 First ever stroke over three months;
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6 Aged between 45 and 75 years;
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9 Be conscious, with stable vital signs;
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11 Ability to walk at least 10 metres without external force and auxiliary equipment;
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14 Written informed consent.
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16 **Exclusion criteria**

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19 Criteria for exclusion are the following:
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22 Have been suffering from brain tumour, brain trauma, brain parasite disease, or
23 other diseases that could cause cognitive impairment;
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27 Severe language, vision, and/or auditory impairment or a neuropsychiatric disorder
28 precluding cognitive examination;
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32 Have been suffering from diseases related to cognitive impairment confirmed by
33 anamnesis, doctors, or families or with a history of cognitive drug use before stroke;
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37 Beck Depression Scale-II score >13;
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41 Patients with alcohol or drug abuse;
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44 Have been suffering from a severe medical condition, such as heart, liver, kidney,
45 and endocrine diseases and haematopoietic system disease;
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47
48 Participating in another clinical trial that would affect the evaluation results of this
49 study.
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52 **Withdrawal or dropout criteria**

Participants in neither the intervention nor control group will be terminated to continue this trial according to the following criteria:

- ① Unwilling to continue this trial;
- ② Suffering from the deterioration of stroke disease or other serious organic diseases during the study period;
- ③ Do not complete the training scheme for four weeks during the study period;
- ④ Those who reject to be measured or followed up;
- ⑤ Suffering from the serious adverse event related to the research.

Recruitment and screening

The recruitment of eligible participants will be conducted by posting up posters on the community publicity column, sending leaflets, and setting up a recruiting station at the Wufeng Community Centre in the Gulou District and the Cangxia Community Centre in the Taijiang District, Fuzhou City. The potentially eligible individuals will first complete a screening to determine their eligibility according to the inclusion and exclusion criteria. Eligible individuals will receive the information about this trial and have an informed discussion with two trained research assistants regarding the information provided. Those who are interested in this study will sign the written informed consent, and the baseline assessment will subsequently be arranged.

Randomization and allocation concealment

After baseline assessment, the eligible participants will be randomly assigned to either the intervention group or the control group with equal rate. The random allocation sequence will be generated using the PLAN procedure of the statistical software SAS v9.0 and be managed by an independent research assistant who is not involved in

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3 recruitment, evaluation and intervention of the participants. The eligible participants
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5 will be informed of their allocation result by the independent research assistant via
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7 telephone.
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10 **Blinding**

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12 In this trial, it is impossible to blind the participants and exercise coaches because this
13
14 trial investigates a non-pharmacological intervention, but two types of blind codes
15
16 will be used to blind the outcome assessors and data statisticians. We will assign an
17
18 independent research manager to be in charge of the random allocation sequence and
19
20 the blind codes. The participants' allocation result (the intervention group or the
21
22 control group) will be replaced using alphabet 'A' or 'B' in the first blind code, and
23
24 the real meaning of 'A' or 'B' will be marked in the second blind code. When the
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26 data-base is locked, the independent research assistant will deliver the group code 'A'
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28 or 'B' of participants to the statistician, and the real meaning of group 'A' or 'B' will
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30 be declared after analysis of all data is completed.
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35 **Intervention**

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38 All participants will continue routine medical or rehabilitative treatment and maintain
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40 usual visits with their primary care physicians throughout the study if necessary.
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42 Meanwhile, all of the participants will also receive the same health education
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44 programme during the intervention period. The Baduanjin exercise will be applied to
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46 the participants in the intervention group, while participants in the control group will
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48 be informed to maintain their usual lifestyle.
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52 The routine medical or rehabilitative treatment will be in accordance with the Chinese
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54 Medical Association's Guidelines for the Prevention and Treatment of
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3 Cerebrovascular Disease in China (2010) [24]. The detailed treatment schedule will be
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5 conducted by their primary care physicians and recorded by the research assistants.
6
7 The health education is conducted by the professional neurologists with a frequency
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9 of once a month and 40 minutes each time. The content of health education primarily
10
11 involves the knowledge of the prevention and rehabilitation of stroke according to
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13 “Out of the Misunderstanding of Stroke Patients’ Rehabilitation” (a bestseller book
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15 for health education after stroke from the Chinese Association of TCM) [25].
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18 **Intervention group**

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21 Participants in the intervention group will receive a 24-week Baduanjin exercise
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23 training, except for the routine medical or rehabilitative treatment and health
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25 education. The Baduanjin exercise training will last for 24 weeks with a frequency of
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27 3 days a week and 40 min a day. The training scheme of Baduanjin exercise originates
28
29 from the ‘Health Qigong Baduanjin Standard’ enacted by the State Sports General
30
31 Administration in 2003 [26]. The whole set of Baduanjin exercise consists of ten
32
33 postures (including the preparation and ending posture) (Figure 3). The participants
34
35 will be gathered together to train when there are more than five participants recruited
36
37 in the same community. Qualified Baduanjin exercise coaches from the Fujian
38
39 University of Traditional Chinese Medicine with more than 5 years of teaching
40
41 experience will be employed to guide participants’ training.
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46 **Control group**

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48 The participants in the control group will not receive any specific exercise training
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50 from the study scheme. These participants will be requested to maintain their original
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52 habit of lifestyle.
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Follow-up

After the 24-week intervention period, all participants will enter an additional 4-week follow-up period. The participants will resume their original lifestyle during the follow-up period. Telephone follow-up or home visiting will be performed once a week by the research assistants. The information on participants' subjective feeling, medications and daily activity, as well as cognitive and motor function, will be recorded or evaluated.

Participant retention and adherence

The success of the intervention is strongly dependent on participants' active participation. To motivate participants' active participation, the staff will use several strategies to improve adherence to the intervention program: ① researchers will explain in detail the benefit of practising Baduanjin exercise after participants are randomly allocated into the intervention group; ② coaches will motivate participants' interest for the Baduanjin exercise training when they instruct participants practising the Baduanjin exercise; and ③ the research assistants will remind participants to practice the Baduanjin exercise according to the study scheme by calling them on the phone. In addition, participant who complete the programme successfully will be rewarded with 100 RMB incentive money. Attendance of the Baduanjin exercise training will be recorded and assessed through records of the proportion of training days. Participants will be marked as absent when they do not attend the training session.

To improve participant retention, once a subject is randomized, the research assistants will make every reasonable effort to ensure the subjects stays for the entire study period. In detail, study assistants will ① maintain participants' interests by interview and phone calls; ② provide periodic communications via materials and talks to inform the participants of our acknowledgement of their support; and ③ be as flexible as

possible with the study schedule in resolving time conflicts with participants' life.

Outcome Assessment

Primary outcome

Global cognitive function will be measured using the Montreal Cognitive Assessment scale (MoCA). The MoCA scale is a brief test to evaluate the global cognitive ability by testing attention, naming, visuospatial/executive function, memory, language, visual structure skills, abstraction, calculation, and orientation with a total score of 0-30 (a higher score equals better function). The Chinese version of the MoCA (Beijing version) was revised and is widely used in China with good validity and reliability^[27]. Primary outcome will be assessed at baseline, 8 weeks, 16 weeks and 24 weeks after intervention and at 28 weeks after a 4-week follow-up period by the neurologists at the Affiliated Rehabilitation Hospital of FJTCM, who will be blinded to the allocation results of participants.

Secondary outcomes

Secondary outcomes involving the specific cognitive domains (i.e., execution, memory, attention, processing speed and visuospatial skill), gait, motor ability, balance ability, activities of daily living and quality of life will be measured at baseline, 24 weeks of intervention and 28 weeks after a 4-week follow-up period by the blinded medical staff or research assistants.

- Executive ability will be assessed using the Trail Making Test (TMT). The TMT consists of two parts, TMT-A and TMT-B: TMT-A requires the participants to sequentially connect 25 encircled numbers on a sheet of paper, while TMT-B requires participants to draw a line alternating between numbers and letters in

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3 ascending order between the number and the letter, and the TMT-B/TMT-A is
4 considered as a valid index of executive ability ^[28].

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8 ● Memory will be measured using the Chinese version of the Auditory Verbal Learning
9 Test (AVLT) ^[29]. AVLT includes three subtests of immediate recall,
10 short-term-delayed recall and long-term delayed recognition. In the immediate
11 recall test, subject will be requested to repeat immediately a list of 15 unrelated
12 words said by the assessor three times; after 15 minutes, subject will be asked to
13 recall the 15 words, and the correct rate is the score of short-term-delayed recall. In
14 the long-term delayed recognition test, a subject is given another list of 15 unrelated
15 words and must recognize the original list of 15 words ^[30]. The Chinese version of
16 the AVLT has been reported reliable with split-half reliability, internal consistency
17 and structure validity ^[29].
- 18
19
20 ● Attention will be measured using the Test of Attention Performance (TAP, V.2.3),
21 which is based on computer-aided neuropsychological tests for assessing the
22 attentional performance ^[31]. Four of this test's sub-tests, including alertness for
23 reaction, general attention, Go/No Go and divided selective attention, will be
24 chosen for this trial.
- 25
26
27 ● Processing speed will be measured by the Digit Symbol Coding (DSC), which is a
28 subtest of the Wechsler Adult Intelligence Scale-Revised China (WAIS-RC) with
29 nine numbers from 1 to 9 and nine corresponding symbols ^[32]. A subject will be
30 asked to draw each symbol under its corresponding number within a 90 s time limit,
31 and the number of correct answers is its scores.
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34 ● Visuospatial ability will be assessed by the Clock Drawing Task (CDT), which is a
35 vision-dependent task ^[33]. The participants will be asked to draw a clock reading a

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3 specific time (generally 11:10). The correctness in clock drawing will be classified
4 according to four categories ^[34].
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8 ● Gait stability and the interactions between cognitive tasks and gait will be measured
9 by gait analysis ^[35]. Participants were instructed to walk in two assigned conditions:
10 free walking as usual and walking as usual with executing a calculation task. The
11 gait parameters in two conditions will be measured with the America Motion
12 Analysis gait analysis system, and the numbers of completion and error rates in
13 calculation tasks will be recorded.
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- 16 ● Motor Function will be evaluated using the Fugl-Meyer Assessment scale (FMA),
17 which is known for its good validity and reliability in evaluating upper and lower
18 limb function after stroke ^[36]. The FMA consists of 50 items based on a six-stage
19 recovery process of Brunnstrom's hemiplegia classification, and 66 points of a
20 possible 100 total score apply to the upper limbs, and the other 34 points are applied
21 to the lower limbs ^[37].
22
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- 24 ● Balance Function will be measured by the Berg Balance Scale (BBS), which
25 consists of a set of 14 tasks to quantitatively assess the static and dynamic balance
26 abilities ^[38]. The BBS is not only one of the most important measurement scales to
27 evaluate the balance function of patients after stroke but can also be used as the risk
28 predictor of accidental fall in stroke patients ^[39].
29
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- 31 ● Activities of Daily Living (ADL) will be assessed using the Modified Barthel
32 Index (MBI), which is a widely used standard scale for assessing functional
33 disability in basic ADL. The MBI contains 10 projects with a total of 100 points,
34 and the higher the score means the better the daily life self-care ability ^[40].
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3 ● Quality of life will be measured by the Medical Outcomes Study 36-Item
4 Short-Form Health Survey (SF-36), which is currently the most commonly used in
5 clinical evaluation of quality of life in the general population and patients. The
6 SF-36 consists of 36 items to assess eight health concepts, and each of them is
7 evaluated separately by the normalized scores from 0 to 100, with the higher score
8 corresponding to better health status^[41]. The Chinese SF-36 has been demonstrated
9 to have high reliability and validity in the Chinese population^[42].
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18 **Safety evaluation**

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20 Although no adverse events are reported currently regarding Baduanjin exercise, any
21 unexpected adverse events during the intervention period will be reported to the
22 research assistants, and causality in relation to the Baduanjin exercise training and the
23 severity of adverse events will be evaluated. Serious adverse events will be reported
24 to the ethics committee immediately.
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33 **Data management and monitoring**

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35 Data will be collected by the outcomes assessors using the print-based case report
36 forms (p-CRFs), and the p-CRFs will later be inputted into the web-based case report
37 forms (w-CRFs) in an electronic data capture system (EDC) by research assistants.
38 The research assistants are also responsible for the integrity and accuracy of data
39 when data are inputted into w-CRFs by means of checking on value ranges, or logical
40 checks. The EDC system and web servers will be provided to the data management
41 centre of FJTCM (<http://210.34.74.191/srtp/users/loginlangth.action>) and meet the
42 available standards for security (the data management centre, which belongs to the
43 Science and Technology Department of FJTCM, is in charge of the monitoring and
44 auditing of all research data in FJTCM). Participants' data in w-CRFs will be stored in
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3 the EDC system in a separate password-protected location. All documents will be
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5 retained securely for five years after completion of the study.
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8 **Statistical analysis**

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10 Statistical analysis will be performed using SPSS 22.0 (IBM, Chicago, IL, USA)
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12 software package by an independent statistician who is not involved in the outcome
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14 assessment, with a two-sided p value <0.05 being considered to be statistically
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16 significant. Continuous variables will be expressed using mean and its standard error
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18 for normal distributions or median and its interquartile range for non-normal
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20 distributions. Categorical variables will be described as frequencies or percentages.
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24 Baseline characteristics between comparison groups will be compared using a t-test or
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26 Mann-Whitney U test for continuous variables and Pearson χ^2 or Fisher's exact test for
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28 categorical variables.
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31 The analysis of primary or secondary outcomes will be based on an intention to treat
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33 (ITT) principle, and the missing data will be imputed using a multiple imputation
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35 method. The group difference between intervention and control group at each time
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37 point (8-week, 16-week, and 24-week after intervention or 4-week follow-up period)
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39 will be analysed using Student's t-test or Mann-Whitney U-test. The linear mixed
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41 model with restricted maximum likelihood will be used to analyse the interaction
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43 effect of Group×Time.
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46 Adverse events (AEs) will be analysed using a chi-square test or Fisher's exact test. If
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48 the formal statistical analyses between-groups cannot be performed due to the lack of
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50 power, AEs will be tabulated and summarized using descriptive statistics.
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54 **Ethics**

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3 This study protocol conformed to the Declaration of Helsinki. Ethics approval of this
4 study protocol, and consent forms were obtained from the Ethics Committee of Fujian
5 University of Traditional Chinese Medicine Subsidiary Rehabilitation Hospital
6 (approval number: 2016KY-022-01). The study background and main objective as
7 well as potential benefits and risks will be fully explained to the participants and their
8 families. Before participating in the study, participants will sign the informed consent
9 document prior to participation.
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17 **Dissemination**

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20 The study protocol has been registered and is available on the Chinese Clinical Trial
21 Registry website (<http://www.chictr.org.cn> with the identifier number ChiCTR-INR-
22 16009364). Study results will be first informed to each participant and later
23 disseminated to researchers, healthcare providers, healthcare professionals and the
24 general public through courses, presentations and the internet, regardless of the
25 magnitude or direction of effect. The results will also be documented in a published
26 peer reviewed academic journal.
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37 **Discussion**

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40 As one of the most common forms of Chinese traditional exercises, Baduanjin
41 exercise consists of eight separate movements, each of which focuses on a different
42 physical area of the body ^[13]. Compared with other aerobic exercises, Baduanjin
43 exercise is not only easy to learn but also is less physical and cognitive demanding ^[43].
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48 Therefore, Baduanjin has become a popular and safe community exercise to promote
49 health in the community of the older population of China. Furthermore, different from
50 other types of aerobic exercise, Baduanjin is also a mind-body exercise combined
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3 with the holistic view and the theory of traditional Chinese medicine in that
4 practitioners are required to reach coordination between mind and body ^[14]. Several
5 studies have reported that regular Baduanjin training has a positive effect in slowing
6 normal age-related memory decline ^[20-21]. Zhu HM et al. even reported that Baduanjin
7 exercise can delay the cognitive impairment progression for the elderly diabetic
8 patients with mild cognitive impairment ^[44]. Therefore, it is reasonable to assume that
9 regular Baduanjin training could be beneficial to cognitive function in stroke patients.
10 This proposed study aims to investigate the effect of Baduanjin exercise on cognitive
11 function, as well as observing the effect on motor function and quality of life in the
12 stroke patients with cognitive impairment. This study will employ rigorousness to
13 control bias, such as randomization, parallel control, and blinding of the outcome
14 assessors and statistician. To ensure participants master standard Baduanjin
15 movements, we will also employ qualified physical exercise teachers to serve as the
16 Baduanjin exercise coaches. However, a potential limitation of this study is that
17 participants and coaches cannot be blinded because it is impossible to make them
18 blinded in non-pharmacological trials ^[45]. Therefore, performance bias may be
19 inevitable, but the exercise coaches will be not involved in the recruitment, outcome
20 assessment, or data analysis of this study. Another challenge that we may encounter
21 for the study is the difficulty in recruiting the eligible stroke patients. Those stroke
22 patients or their families may worry about the exercise risk and prefer to stay in their
23 home and maintain a fairly static life. In addition, a higher dropout rate may also be
24 expected due to the above concerns. To address these problems, we will encourage
25 participants to practice the Baduanjin training at their home after they master this
26 exercise. We also accounted for the higher dropout rate in the sample size estimation
27 to ensure the sufficient statistical power for the study.

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3 In summary, this report describes the first randomized controlled trial to evaluate
4 systematically the rehabilitative effect of Baduanjin exercise on cognitive ability and
5 motor function in stroke patients. This study will determine if Baduanjin training is
6 likely to be effective in improving cognitive function, including global cognitive
7 function and specific cognitive domains, in stroke patients with cognitive impairment.
8 This study will also investigate if Baduanjin training can improve the motor function
9 and quality of life for stroke patients with cognitive impairment and determine if this
10 exercise is acceptable to them. If this trial is successfully conducted and demonstrates
11 a significant result, that intervention would provide an effective rehabilitation
12 approach for stroke patients and adequate supporting evidence for the application of
13 regular Baduanjin exercise in patients with post-stroke cognitive impairment.
14 Conversely, if this exercise training is not effective, the study will identify the factors
15 that contributed to the negative outcome.
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34 **Trial status**

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37 This trial is currently in the recruitment phase.
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43 **Abbreviations**

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46 SD: Standard deviation; DSM-V: Diagnostic and statistical manual disorders, 5th
47 edition; SAS 9.0: Statistical analysis system; TCM: Traditional Chinese medicine;
48 MoCA: Montreal cognitive assessment scale; FJTCM: Fujian University of
49 Traditional Chinese Medicine; TMT: Trail Making Test; AVLT: Auditory verbal
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3 learning test; TAP: Test of attention performance; DSC: Digit symbol coding;
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6 WAIS-RC: Wechsler adult intelligence scale-revised China; CDT: Clock drawing task;
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9 FMA: Fugl-Meyer assessment scale; BBS: Berg balance scale; BI: Barthel index;
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11 ADL: Activities of daily living; SF-36: Item short-form health survey; CRF: Case
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13 report form; EDC: Electronic data capture system; SPSS 22.0: Statistic package for
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15 social science 22.0; ITT: Intention to treat.
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21 **Declarations**

22 **Authors' contributions**

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27 CLD and ZGH conceived and designed of the study protocol and contributed to
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29 drafting the manuscript. ZYH and XZY wrote the manuscript and participated in the
30
31 coordination and implementation of the study. ZGH revised the study protocol and
32
33 wrote several sections of the manuscript. YBZ and TJ helped develop the study
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35 measures and data collection. All authors contributed to drafting the manuscript and
36
37 have read and approved the final version of the manuscript.
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40 **Funding**

41
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43 This study is financially supported by the Shanghai Municipal Commission of Health
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45 and Family Planning (No. 201640127) and the Specialized Research Fund for the Key
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47 Disciplines of Fujian University of Traditional Chinese Medicine
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49 (X2014070-Disciplines).
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52 **Availability of data and materials**

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3 This is not applicable because this is a paper of a study protocol.
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6 **Consent for publication**
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8 Not applicable.
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11 **Competing interests**
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14 None declared.
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16 **Additional files:**
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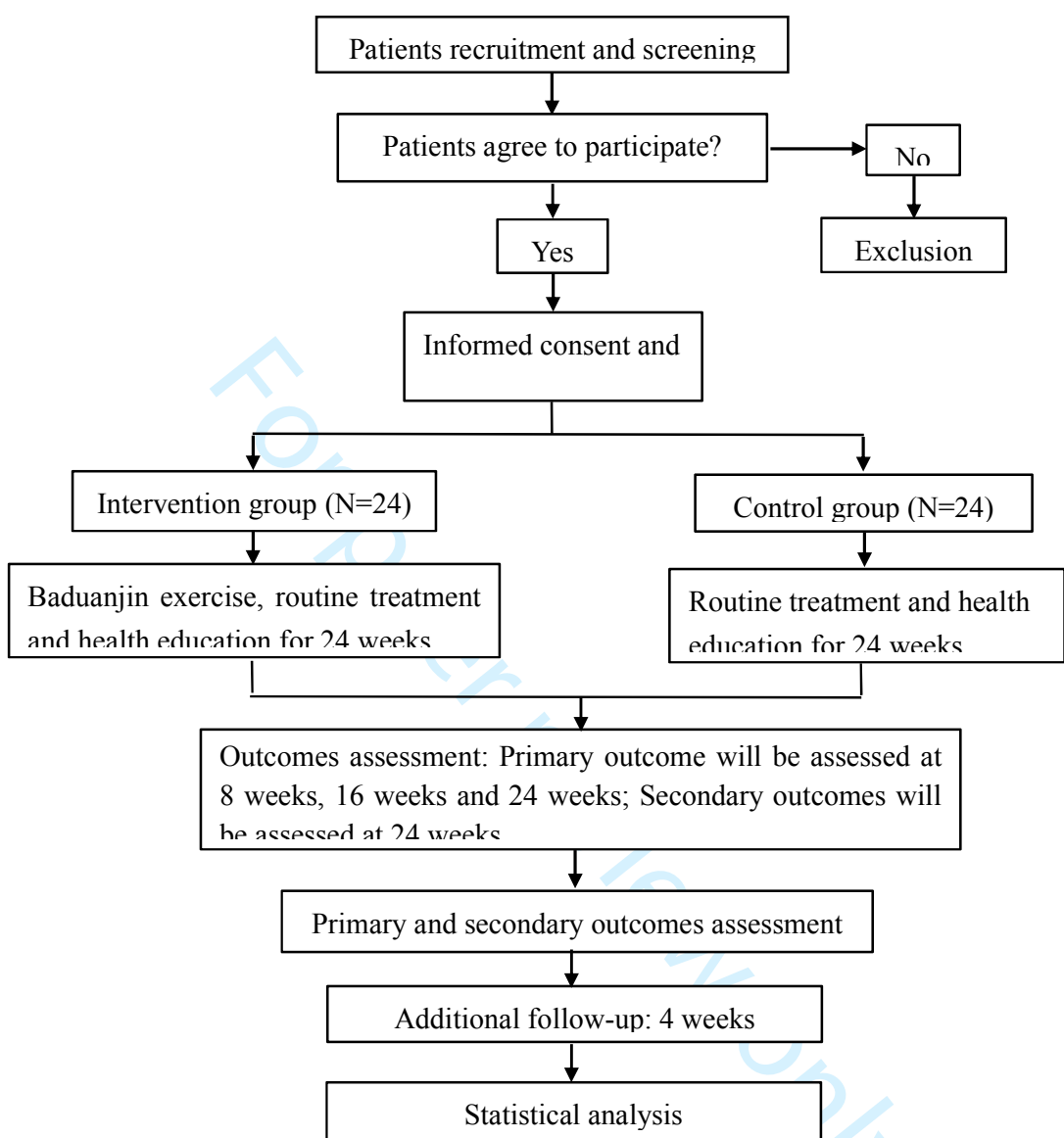
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19 Additional file 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical
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21 trial protocol and related documents.
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24 Additional figure 1: Study design.
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27 Additional figure 2: Schedule of enrolment, interventions, and assessments.
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30 Additional figure 3: Ten postures of Baduanjin.
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Figure 1 Flow diagram of study design

Peer review only

STUDY PERIOD						
	Enrolment	Allocation	Intervention			Follow-up
TIMEPOINT*	$-t_1$	0	t_1	t_2	t_3	t_4
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
ALLOCATION		X				
INTERVENTIONS:						
Intervention group (Baduanjin exercise training+health education)			←————→			
Control group (Health education)			←————→			
ASSESSMENTS:						
Basic characteristics	X					
Global cognitive function	X		X	X	X	X
Executive ability	X		X	X	X	X
Memory	X		X	X	X	X
Attention	X		X	X	X	X
Processing speed	X		X	X	X	X
Visuospatial ability	X		X	X	X	X
Gait stability	X				X	X
Motor Function	X				X	X
Balance Function	X				X	X
Activities of Daily Living	X				X	X
Quality of Life	X				X	X
Adverse events			X	X	X	

<Figure Legend>

* $-t_1 = -2(-1)$ weeks, 0= Baseline, $t_1 =$ Week 8, $t_2 =$ Week 16, $t_3 =$ End of treatment Week 24, $t_4 =$ Follow Up Week 28.

Figure 2: Schedule of enrolment, interventions, and assessments



A: Preparation posture

B: Prop up the sky by two hands to regulate

C: Draw a bow on both sides like shooting a

D: Raise single arm up to regulate spleen (Pi) and stomach (Wei)

E: Look back to treat five strains and seven



F: Look back to treat five strains and seven

G: Pull toes with both hands to reinforce the

H: Clench one's fist and glare to increase

I: Rise and fall on tiptoe seven times to

J: Ending posture

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Figure 2: Ten postures of Baduanjin

For peer review only

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 21
	5b	Name and contact information for the trial sponsor	21
	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	21
	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)	18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	11
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			

1	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	8
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4	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)	7-8
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8	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
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11		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)	11
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14		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
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18		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-11
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21	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	13-16
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27	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)	Figure2
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31	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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34	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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37	Methods: Assignment of interventions (for controlled trials)			
38	Allocation:			
39	Allocation:			
40	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	9
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47	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	9-10
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52	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
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54	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
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1		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
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5	Methods: Data collection, management, and analysis			
6	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	16
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14		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	12&16
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17	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	16
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22	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	17
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26		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
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29		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)	17
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32	Methods: Monitoring			
33	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	16-17
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40		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	9
41				
42				
43				
44	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	16
45				
46				
47	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
48				
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51	Ethics and dissemination			
52	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18
53				
54				
55				

1	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)	18
2				
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4				
5	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
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8		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9 & 16
9				
10				
11	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	16-18
12				
13				
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15	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
16				
17				
18	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	16&18
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22	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	Available in the informed consent materials
23				
24				
25	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	18
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31		31b	Authorship eligibility guidelines and any intended use of professional writers	18
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34		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
35				
36	Appendices			
37				
38	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available in Chinese version
39				
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41	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	Not applicable
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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.

BMJ Open

Effect of Baduanjin exercise on cognitive function in patients with post-stroke cognitive impairment: Study protocol for a randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020954.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Mar-2018
Complete List of Authors:	Zheng, Guohua; Shanghai University of Medicine & Health Sciences, College of Health Information Technology and Management Zheng, Yuhui Xiong, Zhenyu; Fujian University of Traditional Chinese Medicine, College of Rehabilitation Medicine Ye, Bingzhao; Fujian University of Traditional Chinese Medicine, College of Rehabilitation Medicine Tao, Jing; Fujian University of Traditional Chinese Medicine, Department of Physical Education Chen, Lidian; Fujian University of Traditional Chinese Medicine, College of Rehabilitation Medicine
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Reproductive medicine
Keywords:	Baduanjin exercise, cognitive impairment after stroke, randomized controlled trial

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Manuscripts

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3 **Effect of Baduanjin exercise on cognitive function in patients with**
4 **post-stroke cognitive impairment: Study protocol for a randomized**
5 **controlled trial**
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20
21 **Abstract**

22
23 **INTRODUCTION:** Post-stroke cognitive impairment is one of the most common
24 complications in stroke survivors, and over 65% of these patients suffer from
25 cognitive impairment at 12 months following onset, which strongly affects the
26 rehabilitation of their motor function and quality of life. Therefore, it is important to
27 improve the cognitive ability of stroke survivors. As an important component of
28 traditional Chinese Qigong exercises, characterized by the coordination of mind and
29 body with a low exercise intensity, Baduanjin has the potential benefit of improving
30 cognitive ability for stroke patients with cognitive impairment. The primary purpose
31 of this study is to investigate the effectiveness and safety of Baduanjin training on the
32 cognitive function of stroke survivors.
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46 **METHOD AND ANALYSIS:** This study is designed as a randomized, two-arm
47 parallel controlled trial with allocation concealment and assessors blinding. A total of
48 48 participants will be recruited and randomly allocated into the Baduanjin exercise
49 intervention or control group. Baduanjin intervention will last 24 weeks with a
50 frequency of 3 days a week and 40 min a day. Global cognitive function and the
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3 specific domains of cognition (i.e., memory, processing speed, execution, attention
4 and visuospatial ability) will be measured at baseline, 8 weeks, 16 weeks, 24 weeks
5 after intervention and 28 weeks after an additional 4-week follow-up period, while the
6 motor function and quality of life will be measured at baseline, 24 weeks after
7 intervention, and 28 weeks after an additional 4-week follow-up period.
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14 **ETHICS AND DISSEMINATION:** Ethics approval was obtained from the Ethics
15 Committee of Fujian University of Traditional Chinese Medicine Subsidiary
16 Rehabilitation Hospital (approval number: 2016KY-022-01). The findings will be
17 disseminated through peer-reviewed publications and at scientific conferences.
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23 **TRIAL REGISTRATION NUMBER:** ChiCTR-INR-16009364; Pre-results.
24

25
26 Registration date: 10 October, 2016.
27

28 29 **KEYWORDS**

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32 Baduanjin exercise, cognitive impairment after stroke, randomized controlled trial
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40 **Strengths and limitations of this study**

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- 43 ● This protocol presents a rigorous design of a randomized parallel controlled trial
44 that aims to evaluate the effectiveness of Baduanjin exercise on the cognitive
45 function, motor function and quality of life in stroke patients with cognitive
46 impairment.
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 - 49 ● A broad measurement tool and multiple measurement time points will be used to
50 judge the effects of Baduanjin exercise on cognitive ability in stroke patients.
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- If the result we will reach is positive, that will provide a powerful evidence of Baduanjin exercise on improve cognitive function, motor function and quality of life in stroke survivors with cognitive impairment.
- The efficacy of a 24-week Baduanjin exercise intervention in stroke patients with cognitive impairment remains to be determined.

Introduction

Stroke affects 15 million people annually and is a leading cause of death and disability worldwide ^[1]. In China, there are 6 million patients suffering from stroke, and this number increases at an annual rate of 9%. Stroke is associated with many long-term complications, such as motor dysfunction, language dysfunction and cognitive impairment. Post-stroke cognitive impairment is one of most common complications. Approximately 65% of stroke survivors suffer from some extent to cognitive impairment at five years post-stroke, and up to a quarter of those stroke survivors with cognitive impairment are more likely to transition to dementia ^[2], which is associated with increased disability and a poor quality of life ^[3]. As a consequence, it is significant to improve the cognitive function as soon as possible to promote functional recovery and improve quality of life in stroke survivors ^[4].

Theoretically, pharmacological therapy for cognition function may lead to improved recovery. Current data also indicate that a number of drugs may have short-term benefits ^[5-7], but no drug treatment to date has shown convincing clinical

1
2
3 evidence on preventing further cognitive decline or restoring cognitive function for
4 stroke survivors [8]. Thus, increasing attention has been paid to non-drug treatments.
5
6 Aerobic exercises have been widely recognized because of their obvious effect of
7
8 improving cognitive ability in stroke survivors [9-11]. However, most stroke patients do
9
10 not have sufficient compliance to achieve sufficient improvements in aerobic exercise
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12 protocols due to an important concern of safety. Therefore, future stroke studies
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14 involving aerobic exercise training should determine optimal protocols for individuals
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16 with physical limitations [12]. As a mind-body exercise with mild to moderate intensity,
17
18 Baduanjin exercise is one of the most common forms of Qigong that has been
19
20 practised in China for more than 1000 years [13]. Baduanjin exercise consists of eight
21
22 separate and smooth movements and is easier to learn and practice with less limitation
23
24 than other aerobic exercises [14]. Therefore, this exercise is more suitable for older
25
26 adults, especially stroke patients. Increasing studies have demonstrated that regular
27
28 practice of Baduanjin exercise was beneficial to improve the physical and
29
30 psychological outcomes in older people, such as improving blood lipid metabolism
31
32 and sleep quality, lowering blood pressure, reducing depression and anxiety, and
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34 improving physical flexibility [15-19]. Currently, several studies also show that regular
35
36 Baduanjin exercise could slow normal age-related decline in the memory domain, and
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38 delay ageing of intelligence in older adults [20-21]. Consequently, the primary aim of
39
40 this study is to conduct a randomized controlled trial to evaluate systematically the
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42 effect of Baduanjin exercise on the cognitive function in stroke patients with cognitive
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44 impairment.
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50 **Method/Design**

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52 This report describes a two-arm, randomized, parallel controlled trial with allocation
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3 concealment and assessor blinding. The primary purpose is to evaluate the effect of
4
5 Baduanjin on cognitive functions, including global cognitive ability, and primary
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7 cognitive domains, such as memory, attention, and visuospatial ability, in stroke
8
9 patients with cognitive impairment.
10

11
12 This study will be conducted at the Wufeng Community Centre in the Gulou
13
14 District and the Cangxia Community Centre in the Taijiang District, Fuzhou City,
15
16 Fujian, China, which are counterpart support communities of the Affiliated
17
18 Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine. A total
19
20 of 48 eligible participants will be randomly allocated to either the intervention group
21
22 (the Baduanjin exercise group) or the control group (the health education group) in a
23
24 1:1 ratio. The participants in the intervention group will accept Baduanjin exercise
25
26 training intervention three times a week and the routine health education once every
27
28 four weeks for 24 weeks, while those allocated to the control group will only receive
29
30 the routine health education once every four weeks for 24 weeks. Primary and
31
32 secondary outcomes will be measured at baseline, 8 weeks, 16 weeks and 24 weeks
33
34 after intervention and at 28 weeks (after an additional 4-week follow-up period). A
35
36 flow diagram of the study design is shown in Figure 1. The study protocol is reported
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38 according to Standard Protocol Items: Recommendations for Intervention Trials 2013
39
40 (SPIRIT). A SPIRIT Checklist and the schedule of enrolment, interventions and
41
42 assessments are provided in Additional file 1 and Figure 2.
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46
47 Figure 1: Study design.
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50 Additional file 1: SPIRIT 2013 Checklist.
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53 Figure 2: Schedule of enrolment, interventions, and assessments.
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Patient and Public Involvement

This trial is currently in the recruitment phase. No patients and or public has involved in the trial.

Sample size

Sample size was calculated on the basis of the changes in global cognitive ability after 24 weeks of intervention between comparison groups with a significance level of 5% and a two-tailed critical region. The means and their standard deviations (mean \pm SD) of global cognitive ability in the control and aerobic exercise intervention group were 75.93 \pm 4.9 and 81.07 \pm 6.16, respectively, at post-intervention according to the published literature [22]. A sample size of 40 participants was calculated to ensure the same effect size with 80% power by Gpower 3.1.9.2 software. Considering a 20% attrition rate, a total of 48 participants is necessary, with 24 participants being assigned to each group.

Study population

The study population is stroke patients with a diagnosis of cognitive impairment living in Fuzhou City. The inclusion and exclusion criteria for the study sample are as follows.

Inclusion criteria

The eligible participants should meet all of the following criteria:

① Clinical diagnosis of stroke according to the fourth national academic conference on cerebrovascular diseases Diagnostic Criteria for All Kinds of Cerebrovascular Disease [23] and confirmed by computed tomography or magnetic resonance imaging;

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3 Have cognitive impairment diagnosed by Diagnostic and Statistical Manual
4 Disorders (DSM-V);
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8 First ever stroke over three months;
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11 Aged between 45 and 75 years;
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13
14 Be conscious, with stable vital signs;
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17 Ability to walk at least 10 metres without external force and auxiliary equipment;
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19
20 Written informed consent.
21

22 **Exclusion criteria**

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24 Criteria for exclusion are the following:
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27 Have been suffering from brain tumour, brain trauma, brain parasite disease, or
28 other diseases that could cause cognitive impairment;
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32 Severe language, vision, and/or auditory impairment or a neuropsychiatric disorder
33 precluding cognitive examination;
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37 Have been suffering from diseases related to cognitive impairment confirmed by
38 anamnesis, doctors, or families or with a history of cognitive drug use before stroke;
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42 Beck Depression Scale-II score >13;
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45 Patients with alcohol or drug abuse;
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47
48 Have been suffering from a severe medical condition, such as heart, liver, kidney,
49 and endocrine diseases and haematopoietic system disease;
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51
52
53 Participating in another clinical trial that would affect the evaluation results of this
54 study.
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Withdrawal or dropout criteria

Participants in neither the intervention nor control group will be terminated to continue this trial according to the following criteria:

- ① Unwilling to continue this trial;
- ② Suffering from the deterioration of stroke disease or other serious organic diseases during the study period;
- ③ Do not complete the training scheme for four weeks during the study period;
- ④ Those who reject to be measured or followed up;
- ⑤ Suffering from the serious adverse event related to the research.

Recruitment and screening

The recruitment of eligible participants will be conducted by posting up posters on the community publicity column, sending leaflets, and setting up a recruiting station at the Wufeng Community Centre in the Gulou District and the Cangxia Community Centre in the Taijiang District, Fuzhou City. The potentially eligible individuals will first complete a screening to determine their eligibility according to the inclusion and exclusion criteria. Eligible individuals will receive the information about this trial and have an informed discussion with two trained research assistants regarding the information provided. Those who are interested in this study will sign the written informed consent, and the baseline assessment will subsequently be arranged.

Randomization and allocation concealment

After baseline assessment, the eligible participants will be randomly assigned to either the intervention group or the control group with equal rate. The random allocation sequence will be generated using the PLAN procedure of the statistical software SAS

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3 v9.0 and be managed by an independent research assistant who is not involved in
4 recruitment, evaluation and intervention of the participants. The eligible participants
5 will be informed of their allocation result by the independent research assistant via
6 telephone.
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11 **Blinding**

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14 In this trial, it is impossible to blind the participants and exercise coaches because this
15 trial investigates a non-pharmacological intervention, but two types of blind codes
16 will be used to blind the outcome assessors and data statisticians. We will assign an
17 independent research manager to be in charge of the random allocation sequence and
18 the blind codes. The participants' allocation result (the intervention group or the
19 control group) will be replaced using alphabet 'A' or 'B' in the first blind code, and
20 the real meaning of 'A' or 'B' will be marked in the second blind code. When the
21 data-base is locked, the independent research assistant will deliver the group code 'A'
22 or 'B' of participants to the statistician, and the real meaning of group 'A' or 'B' will
23 be declared after analysis of all data is completed.
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37 **Intervention**

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40 All participants will continue routine medical or rehabilitative treatment and maintain
41 usual visits with their primary care physicians throughout the study if necessary.
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43 Meanwhile, all of the participants will also receive the same health education
44 programme during the intervention period. The Baduanjin exercise will be applied to
45 the participants in the intervention group, while participants in the control group will
46 be informed to maintain their usual lifestyle.
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54 The routine medical or rehabilitative treatment will be in accordance with the Chinese
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3 Medical Association's Guidelines for the Prevention and Treatment of
4 Cerebrovascular Disease in China (2010) [24]. The detailed treatment schedule will be
5 conducted by their primary care physicians and recorded by the research assistants.
6
7 The health education is conducted by the professional neurologists with a frequency
8 of once a month and 40 minutes each time. The content of health education primarily
9 involves the knowledge of the prevention and rehabilitation of stroke according to
10 "Out of the Misunderstanding of Stroke Patients' Rehabilitation" (a bestseller book
11 for health education after stroke from the Chinese Association of TCM) [25].
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21 **Intervention group**

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23 Participants in the intervention group will receive a 24-week Baduanjin exercise
24 training, at the same time, they also receive routine medical or rehabilitative treatment
25 and health education. The Baduanjin exercise training will last for 24 weeks with a
26 frequency of 3 days a week and 40 min a day. The training scheme of Baduanjin
27 exercise originates from the 'Health Qigong Baduanjin Standard' enacted by the State
28 Sports General Administration in 2003 [26]. The whole set of Baduanjin exercise
29 consists of ten postures (including the preparation and ending posture) (Figure 3). The
30 participants will be gathered together to train when there are more than five
31 participants recruited in the same community. Qualified Baduanjin exercise coaches
32 from the Fujian University of Traditional Chinese Medicine with more than 5 years of
33 teaching experience will be employed to guide participants' training.
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48 Figure 3: Ten postures of Baduanjin.
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50 **Control group**

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52 The participants in the control group will not receive any specific exercise training
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3 from the study scheme. These participants will be requested to maintain their original
4 habit of lifestyle.
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8 In order to exclude bias from the exceed activity of participants, all participants in
9 both intervention and control group will be required to record an activity log in the
10 intervention period, in which the duration and intensity of their activity in a whole day
11 will be classified into three sections including the duration of low-intensity,
12 moderate-intensity, or high-intensity activities.
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18 19 **Follow-up**

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22 After the 24-week intervention period, all participants will enter an additional 4-week
23 follow-up period. The participants will resume their original lifestyle during the
24 follow-up period. Telephone follow-up or home visiting will be performed once a
25 week by the research assistants. The information on participants' subjective feeling,
26 medications and daily activities will be recorded. The primary and secondary
27 outcomes will be evaluated at end of follow-up period.
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34 35 **Participant retention and adherence**

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38 The success of the intervention is strongly dependent on participants' active
39 participation. To motivate participants' active participation, the staff will use several
40 strategies to improve adherence to the intervention program: ① researchers will
41 explain in detail the benefit of practising Baduanjin exercise after participants are
42 randomly allocated into the intervention group; ② coaches will motivate participants'
43 interest for the Baduanjin exercise training when they instruct participants practising
44 the Baduanjin exercise; and ③ the research assistants will remind participants to
45 practice the Baduanjin exercise according to the study scheme by the WeChat group.
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48 In addition, participant who complete the programme successfully will be rewarded
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3 with 100 RMB incentive money no matter which group they belongs to. Attendance
4 of the Baduanjin exercise training will be recorded and assessed through records of
5 the proportion of training days. Participants will be marked as absent when they do
6 not attend the training session.
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11 To improve participant retention, once a subject is randomized, the research assistants
12 will make every reasonable effort to ensure the subjects stays for the entire study
13 period. In detail, study assistants will □maintain participants' interests by interview
14 and phone calls; □provide periodic communications via materials and talks to inform
15 the participants of our acknowledgement of their support; and □be as flexible as
16 possible with the study schedule in resolving time conflicts with participants' life.
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22 **Outcome Assessment**

23 **Primary outcome**

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28 Global cognitive function will be measured using the Montreal Cognitive Assessment
29 scale (MoCA). The MoCA scale is a brief test to evaluate the global cognitive ability
30 by testing attention, naming, visuospatial/executive function, memory, language,
31 visual structure skills, abstraction, calculation, and orientation with a total score of
32 0-30 (a higher score equals better function). The Chinese version of the MoCA (Beijing
33 version) was revised and is widely used in China with good validity and reliability ^[27].
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39 Primary outcome will be assessed at baseline, 8 weeks, 16 weeks and 24 weeks after
40 intervention and at 28 weeks after a 4-week follow-up period by the neurologists at
41 the Affiliated Rehabilitation Hospital of FJTCM, who will be blinded to the allocation
42 results of participants.
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50 **Secondary outcomes**

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53 Secondary outcomes involving the specific cognitive domains (i.e., execution,
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3 memory, attention, processing speed and visuospatial skill), gait, motor ability,
4 balance ability, activities of daily living and quality of life. Executive ability, memory,
5 attention, Processing speed and visuospatial ability will be measured at baseline, 8
6 weeks, 16 weeks and 24 weeks after intervention and at 28 weeks after a 4-week
7 follow-up period. Gait stability, motor Function, balance function, activities of daily
8 living and quality of life will be assessed at baseline, 24 weeks of intervention and 28
9 weeks after a 4-week follow-up period. All outcome assessments will be measured
10 by the blinded medical staff.
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- 20 ● Executive ability will be assessed using the Trail Making Test (TMT). The TMT
21 consists of two parts, TMT-A and TMT-B: TMT-A requires the participants to
22 sequentially connect 25 encircled numbers on a sheet of paper, while TMT-B
23 requires participants to draw a line alternating between numbers and letters in
24 ascending order between the number and the letter, and the TMT-B/TMT-A is
25 considered as a valid index of executive ability ^[28].
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- 34 ● Memory will be measured using the Chinese version of the Auditory Verbal Learning
35 Test (AVLT) ^[29]. AVLT includes three subtests of immediate recall,
36 short-term-delayed recall and long-term delayed recognition. In the immediate
37 recall test, subject will be requested to repeat immediately a list of 15 unrelated
38 words said by the assessor three times; after 15 minutes, subject will be asked to
39 recall the 15 words, and the correct rate is the score of short-term-delayed recall. In
40 the long-term delayed recognition test, a subject is given another list of 15 unrelated
41 words and must recognize the original list of 15 words ^[30]. The Chinese version of
42 the AVLT has been reported reliable with split-half reliability, internal consistency
43 and structure validity ^[29].
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3 ● Attention will be measured using the Test of Attention Performance (TAP, V.2.3),
4 which is based on computer-aided neuropsychological tests for assessing the
5 attentional performance ^[31]. Four of this test's sub-tests, including alertness for
6 reaction, general attention, Go/No Go and divided selective attention, will be
7 chosen for this trial.
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14 ● Processing speed will be measured by the Digit Symbol Coding (DSC), which is a
15 subtest of the Wechsler Adult Intelligence Scale-Revised China (WAIS-RC) with
16 nine numbers from 1 to 9 and nine corresponding symbols ^[32]. A subject will be
17 asked to draw each symbol under its corresponding number within a 90 s time limit,
18 and the number of correct answers is its scores.
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26 ● Visuospatial ability will be assessed by the Clock Drawing Task (CDT), which is a
27 vision-dependent task ^[33]. The participants will be asked to draw a clock reading a
28 specific time (generally 11:10). The correctness in clock drawing will be classified
29 according to four categories ^[34].
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35 ● Gait stability and the interactions between cognitive tasks and gait will be
36 measured by gait analysis ^[35]. Participants were instructed to walk in two
37 assigned conditions: free walking as usual and walking as usual with executing a
38 calculation task. The gait parameters in two conditions will be measured with the
39 America Motion Analysis gait analysis system, and the numbers of completion
40 and error rates in calculation tasks will be recorded. Those gait parameters mainly
41 comprise of step length (cm), stride length (cm), forward velocity (cm/s), cadence
42 (steps/min), total support time (%), swing time (%), double support time (%),
43 single support time (%) and step width (cm). All these parameters include the
44 affected and unaffected side.
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3 ● Motor Function will be evaluated using the Fugl-Meyer Assessment scale (FMA),
4 which is known for its good validity and reliability in evaluating upper and lower
5 limb function after stroke ^[36]. The FMA consists of 50 items based on a six-stage
6 recovery process of Brunnstrom's hemiplegia classification, and 66 points of a
7 possible 100 total score apply to the upper limbs, and the other 34 points are applied
8 to the lower limbs ^[37].
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16 ● Balance Function will be measured by the Berg Balance Scale (BBS), which
17 consists of a set of 14 tasks to quantitatively assess the static and dynamic balance
18 abilities ^[38]. The BBS is not only one of the most important measurement scales to
19 evaluate the balance function of patients after stroke but can also be used as the risk
20 predictor of accidental fall in stroke patients ^[39].
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28 ● Activities of Daily Living (ADL) will be assessed using the Modified Barthel
29 Index (MBI), which is a widely used standard scale for assessing functional
30 disability in basic ADL. The MBI contains 10 projects with a total of 100 points,
31 and the higher the score means the better the daily life self-care ability ^[40].
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38 ● Quality of life will be measured by the Medical Outcomes Study 36-Item
39 Short-Form Health Survey (SF-36), which is currently the most commonly used in
40 clinical evaluation of quality of life in the general population and patients. The
41 SF-36 consists of 36 items to assess eight health concepts, and each of them is
42 evaluated separately by the normalized scores from 0 to 100, with the higher score
43 corresponding to better health status ^[41]. The Chinese SF-36 has been demonstrated
44 to have high reliability and validity in the Chinese population ^[42].
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53 Safety evaluation

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3 Although no adverse events are reported currently regarding Baduanjin exercise, any
4 unexpected adverse events during the intervention period will be reported to the
5 research assistants, and causality in relation to the Baduanjin exercise training and the
6 severity of adverse events will be evaluated. Serious adverse events will be reported
7 to the ethics committee immediately.
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13 14 **Data management and monitoring** 15

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17 Data will be collected by the outcomes assessors using the print-based case report
18 forms (p-CRFs), and the p-CRFs will later be inputted into the web-based case report
19 forms (w-CRFs) in an electronic data capture system (EDC) by research assistants.
20 The research assistants are also responsible for the integrity and accuracy of data
21 when data are inputted into w-CRFs by means of checking on value ranges, or logical
22 checks. The EDC system and web servers will be provided to the data management
23 centre of FJTCM (<http://210.34.74.191/srtp/users/loginlangth.action>) and meet the
24 available standards for security (the data management centre, which belongs to the
25 Science and Technology Department of FJTCM, is in charge of the monitoring and
26 auditing of all research data in FJTCM). Participants' data in w-CRFs will be stored in
27 the EDC system in a separate password-protected location. All documents will be
28 retained securely for five years after completion of the study.
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43 **Statistical analysis** 44

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46 Statistical analysis will be performed using SPSS 22.0 (IBM, Chicago, IL, USA)
47 software package by an independent statistician who is not involved in the outcome
48 assessment, with a two-sided p value <0.05 being considered to be statistically
49 significant. Continuous variables will be expressed using mean and its standard error
50 for normal distributions or median and its interquartile range for non-normal
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distributions. Categorical variables will be described as frequencies or percentages.

Baseline characteristics between comparison groups will be compared using a t-test or Mann-Whitney U test for continuous variables and Pearson χ^2 or Fisher's exact test for categorical variables.

The analysis of primary or secondary outcomes will be based on an intention to treat (ITT) principle, and the missing data will be imputed using a multiple imputation method. The group difference between intervention and control group at each time point (8-week, 16-week, and 24-week after intervention or 4-week follow-up period) will be analysed using Student's t-test or Mann-Whitney U-test. Linear models or linear regression will be applied to adjust analysis if incomparability of baseline characteristics between groups appears. The linear mixed model with restricted maximum likelihood will be used to analyse the interaction effect of Group \times Time.

Adverse events (AEs) will be analysed using a chi-square test or Fisher's exact test. If the formal statistical analyses between-groups cannot be performed due to the lack of power, AEs will be tabulated and summarized using descriptive statistics.

Ethics

This study protocol conformed to the Declaration of Helsinki. Ethics approval of this study protocol, and consent forms were obtained from the Ethics Committee of Fujian University of Traditional Chinese Medicine Subsidiary Rehabilitation Hospital (approval number: 2016KY-022-01). The study background and main objective as well as potential benefits and risks will be fully explained to the participants and their families. Before participating in the study, participants will sign the informed consent document prior to participation.

Dissemination

The study protocol has been registered and is available on the Chinese Clinical Trial Registry website (<http://www.chictr.org.cn> with the identifier number ChiCTR-INR-16009364). Study results will be first informed to each participant and later disseminated to researchers, healthcare providers, healthcare professionals and the general public through courses, presentations and the internet, regardless of the magnitude or direction of effect. The results will also be documented in a published peer reviewed academic journal.

Discussion

As one of the most common forms of Chinese traditional exercises, Baduanjin exercise consists of eight separate movements, each of which focuses on a different physical area of the body ^[13]. Compared with other aerobic exercises, Baduanjin exercise is not only easy to learn but also is less physical and cognitive demanding ^[43]. Therefore, Baduanjin has become a popular and safe community exercise to promote health in the community of the older population of China. Furthermore, different from other types of aerobic exercise, Baduanjin is also a mind-body exercise combined with the holistic view and the theory of traditional Chinese medicine in that practitioners are required to reach coordination between mind and body ^[14]. Several studies have reported that regular Baduanjin training has a positive effect in slowing normal age-related memory decline ^[20-21]. Zhu HM et al. even reported that Baduanjin exercise can delay the cognitive impairment progression for the elderly diabetic patients with mild cognitive impairment ^[44]. Therefore, it is reasonable to assume that regular Baduanjin training could be beneficial to cognitive function in stroke patients. This proposed study aims to investigate the effect of Baduanjin exercise on cognitive

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3 function, as well as observing the effect on motor function and quality of life in the
4 stroke patients with cognitive impairment. This study will employ rigorousness to
5 control bias, such as randomization, parallel control, and blinding of the outcome
6 assessors and statistician. To ensure participants master standard Baduanjin
7 movements, we will also employ qualified physical exercise teachers to serve as the
8 Baduanjin exercise coaches. However, a potential limitation of this study is that
9 participants and coaches cannot be blinded because it is impossible to make them
10 blinded in non-pharmacological trials ^[45]. Therefore, performance bias may be
11 inevitable, but the exercise coaches will be not involved in the recruitment, outcome
12 assessment, or data analysis of this study. Another challenge that we may encounter
13 for the study is the difficulty in recruiting the eligible stroke patients. Those stroke
14 patients or their families may worry about the exercise risk and prefer to stay in their
15 home and maintain a fairly static life. In addition, a higher dropout rate may also be
16 expected due to the above concerns. To address these problems, we will encourage
17 participants to practice the Baduanjin training at their home after they master this
18 exercise. We also accounted for the higher dropout rate in the sample size estimation
19 to ensure the sufficient statistical power for the study.
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40 In summary, this report describes the first randomized controlled trial to evaluate
41 systematically the rehabilitative effect of Baduanjin exercise on cognitive ability and
42 motor function in stroke patients. This study will determine if Baduanjin training is
43 likely to be effective in improving cognitive function, including global cognitive
44 function and specific cognitive domains, in stroke patients with cognitive impairment.
45 This study will also investigate if Baduanjin training can improve the motor function
46 and quality of life for stroke patients with cognitive impairment and determine if this
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3 exercise is acceptable to them. If this trial is successfully conducted and demonstrates
4 a significant result, that intervention would provide an effective rehabilitation
5 approach for stroke patients and adequate supporting evidence for the application of
6 regular Baduanjin exercise in patients with post-stroke cognitive impairment.
7 Conversely, if this exercise training is not effective, the study will identify the factors
8 that contributed to the negative outcome.
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19 **Trial status**

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21 This trial is currently in the recruitment phase.
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28 **Abbreviations**

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31 SD: Standard deviation; DSM-V: Diagnostic and statistical manual disorders, 5th
32 edition; SAS 9.0: Statistical analysis system; TCM: Traditional Chinese medicine;
33 MoCA: Montreal cognitive assessment scale; FJTCM: Fujian University of
34 Traditional Chinese Medicine; TMT: Trail Making Test; AVLT: Auditory verbal
35 learning test; TAP: Test of attention performance; DSC: Digit symbol coding;
36 WAIS-RC: Wechsler adult intelligence scale-revised China; CDT: Clock drawing task;
37 FMA: Fugl-Meyer assessment scale; BBS: Berg balance scale; BI: Barthel index;
38 ADL: Activities of daily living; SF-36: Item short-form health survey; CRF: Case
39 report form; EDC: Electronic data capture system; SPSS 22.0: Statistic package for
40 social science 22.0; ITT: Intention to treat.
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Declarations

Authors' contributions

CLD and ZGH conceived and designed of the study protocol and contributed to drafting the manuscript. ZYH and XZY wrote the manuscript and participated in the coordination and implementation of the study. ZGH revised the study protocol and wrote several sections of the manuscript. YBZ and TJ helped develop the study measures and data collection. All authors contributed to drafting the manuscript and have read and approved the final version of the manuscript.

Funding

This study is financially supported by the Shanghai Municipal Commission of Health and Family Planning (No. 201640127) and the Specialized Research Fund for the Key Disciplines of Fujian University of Traditional Chinese Medicine (X2014070-Disciplines).

Availability of data and materials

This is not applicable because this is a paper of a study protocol.

Consent for publication

Not applicable.

Competing interests

None declared.

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3 **Additional files:**
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5 Additional file 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical
6 trial protocol and related documents.
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10 Additional figure 1: Study design.
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13 Additional figure 2: Schedule of enrolment, interventions, and assessments.
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16 Additional figure 3: Ten postures of Baduanjin.
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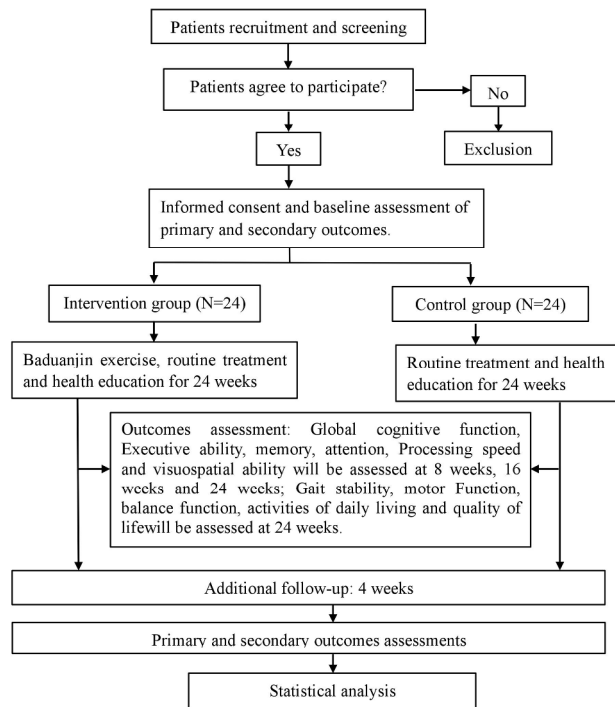


Figure 1 Flow diagram of study design

210x297mm (300 x 300 DPI)

STUDY PERIOD						
	Enrolment	Allocation	Intervention			Follow-up
TIMEPOINT*	- t_1	0	t_1	t_2	t_3	t_4
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
ALLOCATION						
		X				
INTERVENTIONS:						
Intervention group (Baduanjin exercise training+health education)			←————→			
Control group (Health education)			←————→			
ASSESSMENTS:						
Basic characteristics	X					
Global cognitive function	X		X	X	X	X
Executive ability	X		X	X	X	X
Memory	X		X	X	X	X
Attention	X		X	X	X	X
Processing speed	X		X	X	X	X
Visuospatial ability	X		X	X	X	X
Gait stability	X				X	X
Motor Function	X				X	X
Balance Function	X				X	X
Activities of Daily Living	X				X	X
Quality of Life	X				X	X
Adverse events			X	X	X	

<Figure Legend>

* - t_1 = -2(-1) weeks, 0 = Baseline, t_1 = Week 8, t_2 = Week 16, t_3 = End of treatment Week 24, t_4 = Follow Up Week 28.

Figure 2: Schedule of enrolment, interventions, and assessments

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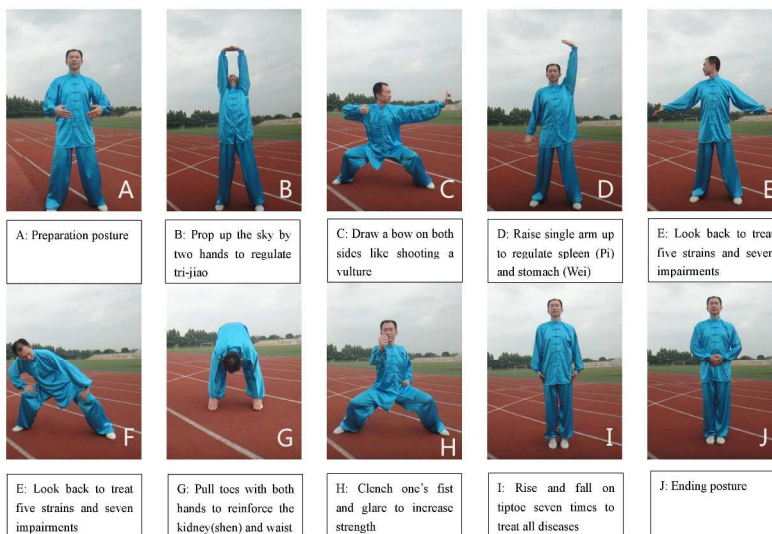


Figure 3: Ten postures of Baduanjin

297x210mm (300 x 300 DPI)

new only



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	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 21
	5b	Name and contact information for the trial sponsor	21
	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	21
	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)	18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	11
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			

1	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	8
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4	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)	7-8
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8	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
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11		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)	11
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14		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
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18		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-11
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21	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	13-16
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27	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)	Figure2
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31	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
32				
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34	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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37	Methods: Assignment of interventions (for controlled trials)			
38	Allocation:			
39	Allocation:			
40	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	9
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47	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	9-10
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52	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
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55	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
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1		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
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5	Methods: Data collection, management, and analysis			
6	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	16
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14		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	12&16
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17	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	16
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22	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	17
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26		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
27				
28				
29		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)	17
30				
31				
32	Methods: Monitoring			
33	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	16-17
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40		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	9
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44	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	16
45				
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47	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
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51	Ethics and dissemination			
52	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18
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1	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)	18
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5	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
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7				
8		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9&16
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10				
11	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	16-18
12				
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15	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
16				
17				
18	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	16&18
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21	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	Available in the informed consent materials
22				
23				
24				
25	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	18
26				
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31		31b	Authorship eligibility guidelines and any intended use of professional writers	18
32				
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34		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
35				
36	Appendices			
37				
38	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available in Chinese version
39				
40				
41	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	Not applicable
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43				

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)” license.

BMJ Open

Effect of Baduanjin exercise on cognitive function in patients with post-stroke cognitive impairment: Study protocol for a randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020954.R2
Article Type:	Protocol
Date Submitted by the Author:	25-Apr-2018
Complete List of Authors:	Zheng, Guohua; Shanghai University of Medicine & Health Sciences, College of Health Information Technology and Management Zheng, Yuhui Xiong, Zhenyu; Fujian University of Traditional Chinese Medicine, College of Rehabilitation Medicine Ye, Bingzhao; Fujian University of Traditional Chinese Medicine, College of Rehabilitation Medicine Tao, Jing; Fujian University of Traditional Chinese Medicine, Department of Physical Education Chen, Lidian; Fujian University of Traditional Chinese Medicine, College of Rehabilitation Medicine
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Reproductive medicine
Keywords:	Baduanjin exercise, cognitive impairment after stroke, randomized controlled trial

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3 **Effect of Baduanjin exercise on cognitive function in patients with**
4 **post-stroke cognitive impairment: Study protocol for a randomized**
5 **controlled trial**
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7

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17 paper.

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22
23 **Abstract**

24
25 **INTRODUCTION:** Post-stroke cognitive impairment is one of the most common
26 complications in stroke survivors, and over 65% of these patients suffer from
27 cognitive impairment at 12 months following onset, which strongly affects the
28 rehabilitation of their motor function and quality of life. Therefore, it is important to
29 improve the cognitive ability of stroke survivors. As an important component of
30 traditional Chinese Qigong exercises, characterized by the coordination of mind and
31 body with a low exercise intensity, Baduanjin has the potential benefit of improving
32 cognitive ability for stroke patients with cognitive impairment. The primary purpose
33 of this study is to investigate the effectiveness and safety of Baduanjin training on the
34 cognitive function of stroke survivors.

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48 **METHOD AND ANALYSIS:** This study is designed as a randomized, two-arm
49 parallel controlled trial with allocation concealment and assessors blinding. A total of
50 48 participants will be recruited and randomly allocated into the Baduanjin exercise
51 intervention or control group. Baduanjin intervention will last 24 weeks with a

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3 frequency of 3 days a week and 40 min a day. Global cognitive function and the
4
5 specific domains of cognition (i.e., memory, processing speed, execution, attention
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7 and visuospatial ability) will be measured at baseline, 8-, 16-, 24-week after
8
9 intervention and after an additional 4-week follow-up period, while the motor
10
11 function and quality of life will be measured at baseline, 24-week after intervention,
12
13 and after an additional 4-week follow-up period.
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16 **ETHICS AND DISSEMINATION:** Ethics approval was obtained from the Ethics
17
18 Committee of Fujian University of Traditional Chinese Medicine Subsidiary
19
20 Rehabilitation Hospital (approval number: 2016KY-022-01). The findings will be
21
22 disseminated through peer-reviewed publications and at scientific conferences.
23
24

25 **TRIAL REGISTRATION NUMBER:** ChiCTR-INR-16009364; Pre-results.
26
27

28 Registration date: 10 October, 2016.
29
30

31 **KEYWORDS**

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34 Baduanjin exercise, cognitive impairment after stroke, randomized controlled trial
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45 **Strengths and limitations of this study**

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- 45 ● This protocol presents a rigorous design of a randomized parallel controlled trial
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47 that aims to evaluate the effectiveness of Baduanjin exercise on the cognitive
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49 function, motor function and quality of life in stroke patients with cognitive
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51 impairment.
52
- 54 ● A broad measurement tool and multiple measurement time points will be used to
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3 judge the effects of Baduanjin exercise on cognitive ability in stroke patients.
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- 5 ● If the result we will reach is positive, that will provide a powerful evidence of
6 Baduanjin exercise on improve cognitive function, motor function and quality of
7 life in stroke survivors with cognitive impairment.
8
- 9 ● The efficacy of a 24-week Baduanjin exercise intervention in stroke patients with
10 cognitive impairment remains to be determined.
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26 **Introduction**

27
28 Stroke affects 15 million people annually and is a leading cause of death and
29 disability worldwide ^[1]. In China, there are 6 million patients suffering from stroke,
30 and this number increases at an annual rate of 9%. Stroke is associated with many
31 long-term complications, such as motor dysfunction, language dysfunction and
32 cognitive impairment. Post-stroke cognitive impairment is one of most common
33 complications. Approximately 65% of stroke survivors suffer from some extent to
34 cognitive impairment at five years post-stroke, and up to a quarter of those stroke
35 survivors with cognitive impairment are more likely to transition to dementia ^[2],
36 which is associated with increased disability and a poor quality of life ^[3]. As a
37 consequence, it is significant to improve the cognitive function as soon as possible to
38 promote functional recovery and improve quality of life in stroke survivors ^[4].
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53 Theoretically, pharmacological therapy for cognition function may lead to
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3 improved recovery. Current data also indicate that a number of drugs may have
4 short-term benefits ^[5-7], but no drug treatment to date has shown convincing clinical
5 evidence on preventing further cognitive decline or restoring cognitive function for
6 stroke survivors ^[8]. Thus, increasing attention has been paid to non-drug treatments.
7
8 Aerobic exercises have been widely recognized because of their obvious effect of
9 improving cognitive ability in stroke survivors ^[9-11]. However, most stroke patients do
10 not have sufficient compliance to achieve sufficient improvements in aerobic exercise
11 protocols due to an important concern of safety. Therefore, future stroke studies
12 involving aerobic exercise training should determine optimal protocols for individuals
13 with physical limitations ^[12]. As a mind-body aerobic exercise with mild to moderate
14 intensity, Baduanjin exercise has an emphasis on a combination of symmetrical
15 physical postures, meditative mind, and breathing techniques in a harmonious manner,
16 and is one of the most common forms of Qigong that has been practised in China for
17 more than 1000 years ^[13]. Compared to complex and lengthy exercise form such as
18 Tai Chi, Baduanjin exercise only consists of eight separate and smooth movements
19 which is less physically and cognitively demanding, and is easier to learn and practice
20 with less limitation ^[13-14]. Therefore, this exercise is more suitable for older adults,
21 especially stroke patients. Increasing studies have demonstrated that regular practice
22 of Baduanjin exercise was beneficial to improve the physical and psychological
23 outcomes in older people, such as improving blood lipid metabolism and sleep quality,
24 lowering blood pressure, reducing depression and anxiety, and improving physical
25 flexibility ^[15-19]. Currently, several studies also show that regular Baduanjin exercise
26 could slow normal age-related decline in the memory domain, and delay ageing of
27 intelligence in older adults ^[20-21]. Consequently, the primary aim of this study is to
28 conduct a randomized controlled trial to evaluate systematically the effect of
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3 Baduanjin exercise on the cognitive function in stroke patients with cognitive
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5 impairment.
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7 8 **Method/Design** 9

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11 This report describes a two-arm, randomized, parallel controlled trial with allocation
12 concealment and assessor blinding. The primary purpose is to evaluate the effect of
13 Baduanjin on cognitive functions, including global cognitive ability, and primary
14 cognitive domains, such as memory, attention, and visuospatial ability, in stroke
15 patients with cognitive impairment.
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22 This study will be conducted at the Wufeng Community Centre in the Gulou
23 District and the Cangxia Community Centre in the Taijiang District, Fuzhou City,
24 Fujian, China, which are counterpart support communities of the Affiliated
25 Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine. A total
26 of 48 eligible participants will be randomly allocated to either the intervention group
27 (the Baduanjin exercise group) or the control group (the health education group) in a
28 1:1 ratio. The participants in the intervention group will accept Baduanjin exercise
29 training intervention three times a week and the routine health education once every
30 four weeks for 24 weeks, while those allocated to the control group will only receive
31 the routine health education once every four weeks for 24 weeks. Primary and
32 secondary outcomes will be measured at baseline, 8-, 16- and 24-week after
33 intervention and after an additional 4-week follow-up period. A flow diagram of the
34 study design is shown in Figure 1. The study protocol is reported according to
35 Standard Protocol Items: Recommendations for Intervention Trials 2013 (SPIRIT). A
36 SPIRIT Checklist and the schedule of enrolment, interventions and assessments are
37 provided in Additional file 1 and Figure 2.
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3 Figure 1: Study design.
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5 Additional file 1: SPIRIT 2013 Checklist.
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8 Figure 2: Schedule of enrolment, interventions, and assessments.
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10 11 **Patient and Public Involvement** 12

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14 This trial is currently in the recruitment phase. No patients and or public has involved
15 in the trial.
16
17

18 19 **Sample size** 20

21 Sample size was calculated on the basis of the changes in global cognitive ability after
22 24 weeks of intervention between comparison groups with a significance level of 5%
23 and a two-tailed critical region. The means and their standard deviations (mean \pm SD)
24 of global cognitive ability in the control and aerobic exercise intervention group were
25 75.93 \pm 4.9 and 81.07 \pm 6.16, respectively, at post-intervention according to the
26 published literature ^[22]. A sample size of 40 participants was calculated to ensure the
27 same effect size with 80% power by Gpower 3.1.9.2 software. Considering a 20%
28 attrition rate, a total of 48 participants is necessary, with 24 participants being
29 assigned to each group.
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42 43 **Study population** 44

45 The study population is stroke patients with a diagnosis of cognitive impairment
46 living in Fuzhou City. The inclusion and exclusion criteria for the study sample are as
47 follows.
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51 52 **Inclusion criteria** 53

54 The eligible participants should meet all of the following criteria:
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3 Clinical diagnosis of stroke according to the fourth national academic conference on
4 cerebrovascular diseases Diagnostic Criteria for All Kinds of Cerebrovascular Disease
5 [23] and confirmed by computed tomography or magnetic resonance imaging;
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10 Have cognitive impairment diagnosed by Diagnostic and Statistical Manual
11 Disorders (DSM-V);
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15 First ever stroke over three months;
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18 Aged between 45 and 75 years;
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21 Be conscious, with stable vital signs;
22
23
24 Ability to walk at least 10 metres without external force and auxiliary equipment;
25
26 Written informed consent.

27 28 29 **Exclusion criteria**

30
31 Criteria for exclusion are the following:

- 32
33
34 Have been suffering from brain tumour, brain trauma, brain parasite disease, or
35 other diseases that could cause cognitive impairment;
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39 Severe language, vision, and/or auditory impairment or a neuropsychiatric disorder
40 precluding cognitive examination;
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44 Have been suffering from diseases related to cognitive impairment confirmed by
45 anamnesis, doctors, or families or with a history of cognitive drug use before stroke;
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49 Beck Depression Scale-II score >13;
50
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52 Patients with alcohol or drug abuse;
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54
55 Have been suffering from a severe medical condition, such as heart, liver, kidney,

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3 and endocrine diseases and haematopoietic system disease;

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5 Participating in another clinical trial that would affect the evaluation results of this
6
7 study.
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10 **Withdrawal or dropout criteria**

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13 Participants in neither the intervention nor control group will be terminated to
14
15 continue this trial according to the following criteria:
16

- 17
18 ① Unwilling to continue this trial;
19
20 ② Suffering from the deterioration of stroke disease or other serious organic diseases
21 during the study period;
22
23 ③ Do not complete the training scheme for four weeks during the study period;
24
25 ④ Those who reject to be measured or followed up;
26
27 ⑤ Suffering from the serious adverse event related to the research.
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32 **Recruitment and screening**

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34 The recruitment of eligible participants will be conducted by posting up posters on the
35
36 community publicity column, sending leaflets, and setting up a recruiting station at
37
38 the Wufeng Community Centre in the Gulou District and the Cangxia Community
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40 Centre in the Taijiang District, Fuzhou City. The potentially eligible individuals will
41
42 first complete a screening to determine their eligibility according to the inclusion and
43
44 exclusion criteria. Eligible individuals will receive the information about this trial and
45
46 have an informed discussion with two trained research assistants regarding the
47
48 information provided. Those who are interested in this study will sign the written
49
50 informed consent, and the baseline assessment will subsequently be arranged.
51
52
53

54 **Randomization and allocation concealment**

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3 After baseline assessment, the eligible participants will be randomly assigned to either
4 the intervention group or the control group with equal rate. The random allocation
5 sequence will be generated using the PLAN procedure of the statistical software SAS
6 v9.0 and be managed by an independent research assistant who is not involved in
7 recruitment, evaluation and intervention of the participants. The eligible participants
8 will be informed of their allocation result by the independent research assistant via
9 telephone.
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18 **Blinding**

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21 In this trial, it is impossible to blind the participants and exercise coaches because this
22 trial investigates a non-pharmacological intervention, but two types of blind codes
23 will be used to blind the outcome assessors and data statisticians. We will assign an
24 independent research manager to be in charge of the random allocation sequence and
25 the blind codes. The participants' allocation result (the intervention group or the
26 control group) will be replaced using alphabet 'A' or 'B' in the first blind code, and
27 the real meaning of 'A' or 'B' will be marked in the second blind code. When the
28 data-base is locked, the independent research assistant will deliver the group code 'A'
29 or 'B' of participants to the statistician, and the real meaning of group 'A' or 'B' will
30 be declared after analysis of all data is completed.
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44 **Intervention**

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47 All participants will continue routine medical or rehabilitative treatment and maintain
48 usual visits with their primary care physicians throughout the study if necessary.
49 Meanwhile, all of the participants will also receive the same health education
50 programme during the intervention period. The Baduanjin exercise will be applied to
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3 the participants in the intervention group, while participants in the control group will
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5 be informed to maintain their usual lifestyle.
6

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8 The routine medical or rehabilitative treatment will be in accordance with the Chinese
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10 Medical Association's Guidelines for the Prevention and Treatment of
11
12 Cerebrovascular Disease in China (2010) [24]. The detailed treatment schedule will be
13
14 conducted by their primary care physicians and recorded by the research assistants.
15
16 The health education is conducted by the professional neurologists with a frequency
17
18 of once a month and 40 minutes each time. The content of health education primarily
19
20 involves the knowledge of the prevention and rehabilitation of stroke according to
21
22 "Out of the Misunderstanding of Stroke Patients' Rehabilitation" (a bestseller book
23
24 for health education after stroke from the Chinese Association of TCM) [25].
25
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27 28 **Intervention group**

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30 Participants in the intervention group will receive a 24-week Baduanjin exercise
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32 training, at the same time, they also receive routine medical or rehabilitative treatment
33
34 and health education. The Baduanjin exercise training will last for 24 weeks with a
35
36 frequency of 3 days a week and 40 min a day. The training scheme of Baduanjin
37
38 exercise originates from the 'Health Qigong Baduanjin Standard' enacted by the State
39
40 Sports General Administration in 2003 [26]. The whole set of Baduanjin exercise
41
42 consists of ten postures (including the preparation and ending posture) (Figure 3). The
43
44 participants will be gathered together to train when there are more than five
45
46 participants recruited in the same community. Qualified Baduanjin exercise coaches
47
48 from the Fujian University of Traditional Chinese Medicine with more than 5 years of
49
50 teaching experience will be employed to guide participants' training.
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54
55 Figure 3: Ten postures of Baduanjin.

Control group

The participants in the control group will not receive any specific exercise training from the study scheme. These participants will be requested to maintain their original habit of lifestyle.

In order to exclude bias from the exceed activity of participants, all participants in both intervention and control group will be required to record an activity log in the intervention period, in which the duration and intensity of their activity in a whole day will be classified into three sections including the duration of low-intensity, moderate-intensity, or high-intensity activities.

Follow-up

After the 24-week intervention period, all participants will enter an additional 4-week follow-up period. The participants will resume their original lifestyle during the follow-up period. Telephone follow-up or home visiting will be performed once a week by the research assistants. The information on participants' subjective feeling, medications and daily activities will be recorded. The primary and secondary outcomes will be evaluated at end of follow-up period.

Participant retention and adherence

The success of the intervention is strongly dependent on participants' active participation. To motivate participants' active participation, the staff will use several strategies to improve adherence to the intervention program: ① researchers will explain in detail the benefit of practising Baduanjin exercise after participants are randomly allocated into the intervention group; ② coaches will motivate participants' interest for the Baduanjin exercise training when they instruct participants practising the Baduanjin exercise; and ③ the research assistants will remind participants to

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3 practice the Baduanjin exercise according to the study scheme by the WeChat group.
4
5 In addition, participant who complete the programme successfully will be rewarded
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7 with 100 RMB incentive money no matter which group they belongs to. Attendance
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9 of the Baduanjin exercise training will be recorded and assessed through records of
10
11 the proportion of training days. Participants will be marked as absent when they do
12
13 not attend the training session.

14
15 To improve participant retention, once a subject is randomized, the research assistants
16
17 will make every reasonable effort to ensure the subjects stays for the entire study
18
19 period. In detail, study assistants will □maintain participants' interests by interview
20
21 and phone calls; □provide periodic communications via materials and talks to inform
22
23 the participants of our acknowledgement of their support; and □be as flexible as
24
25 possible with the study schedule in resolving time conflicts with participants' life.

26 **Outcome Assessment**

27 **Primary outcome**

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32 Global cognitive function will be measured using the Montreal Cognitive Assessment
33
34 scale (MoCA). The MoCA scale is a brief test to evaluate the global cognitive ability
35
36 by testing attention, naming, visuospatial/executive function, memory, language,
37
38 visual structure skills, abstraction, calculation, and orientation with a total score of
39
40 0-30 (a higher score equals better function). The Chinese version of the MoCA (Beijing
41
42 version) was revised and is widely used in China with good validity and reliability ^[27].
43
44
45 Primary outcome will be assessed at baseline, 8 weeks, 16 weeks and 24 weeks after
46
47 intervention and after an additional 4-week follow-up period by the neurologists at the
48
49 Affiliated Rehabilitation Hospital of FJTCM, who will be blinded to the allocation
50
51 results of participants.
52

53 **Secondary outcomes**

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3 Secondary outcomes involving the specific cognitive domains (i.e., execution,
4 memory, attention, processing speed and visuospatial skill), gait, motor ability,
5 balance ability, activities of daily living and quality of life. Executive ability, memory,
6 attention, Processing speed and visuospatial ability will be measured at baseline, 8
7 weeks, 16 weeks and 24 weeks after intervention and after an additional 4-week
8 follow-up period. Gait stability, motor Function, balance function, activities of daily
9 living and quality of life will be assessed at baseline, 24 weeks of intervention and
10 after an additional 4-week follow-up period. All outcome assessments will be
11 measured by the blinded medical staff.
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23 ● Executive ability will be assessed using the Trail Making Test (TMT). The TMT
24 consists of two parts, TMT-A and TMT-B: TMT-A requires the participants to
25 sequentially connect 25 encircled numbers on a sheet of paper, while TMT-B
26 requires participants to draw a line alternating between numbers and letters in
27 ascending order between the number and the letter, and the TMT-B/TMT-A is
28 considered as a valid index of executive ability^[28].
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- 36 ● Memory will be measured using the Chinese version of the Auditory Verbal Learning
37 Test (AVLT)^[29]. AVLT includes three subtests of immediate recall,
38 short-term-delayed recall and long-term delayed recognition. In the immediate
39 recall test, subject will be requested to repeat immediately a list of 15 unrelated
40 words said by the assessor three times; after 15 minutes, subject will be asked to
41 recall the 15 words, and the correct rate is the score of short-term-delayed recall. In
42 the long-term delayed recognition test, a subject is given another list of 15 unrelated
43 words and must recognize the original list of 15 words^[30]. The Chinese version of
44 the AVLT has been reported reliable with split-half reliability, internal consistency
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3 and structure validity ^[29].
4

- 5 ● Attention will be measured using the Test of Attention Performance (TAP, V.2.3),
6 which is based on computer-aided neuropsychological tests for assessing the
7 attentional performance ^[31]. Four of this test's sub-tests, including alertness for
8 reaction, general attention, Go/No Go and divided selective attention, will be
9 chosen for this trial.
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- 16 ● Processing speed will be measured by the Digit Symbol Coding (DSC), which is a
17 subtest of the Wechsler Adult Intelligence Scale-Revised China (WAIS-RC) with
18 nine numbers from 1 to 9 and nine corresponding symbols ^[32]. A subject will be
19 asked to draw each symbol under its corresponding number within a 90 s time limit,
20 and the number of correct answers is its scores.
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- 27 ● Visuospatial ability will be assessed by the Clock Drawing Task (CDT), which is a
28 vision-dependent task ^[33]. The participants will be asked to draw a clock reading a
29 specific time (generally 11:10). The correctness in clock drawing will be classified
30 according to four categories ^[34].
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- 37 ● Gait stability and the interactions between cognitive tasks and gait will be
38 measured by gait analysis ^[35]. Participants were instructed to walk in two
39 assigned conditions: free walking as usual and walking as usual with executing a
40 calculation task. The gait parameters in two conditions will be measured with the
41 America Motion Analysis gait analysis system, and the numbers of completion
42 and error rates in calculation tasks will be recorded. Those gait parameters mainly
43 comprise of step length (cm), stride length (cm), forward velocity (cm/s), cadence
44 (steps/min), total support time (%), swing time (%), double support time (%),
45 single support time (%) and step width (cm). All these parameters include the
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3 affected and unaffected side.
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- 5 ● Motor function will be evaluated using the Fugl-Meyer Assessment scale (FMA),
6 which is known for its good validity and reliability in evaluating upper and lower
7 limb function after stroke ^[36]. The FMA consists of 50 items based on a six-stage
8 recovery process of Brunnstrom's hemiplegia classification, and 66 points of a
9 possible 100 total score apply to the upper limbs, and the other 34 points are applied
10 to the lower limbs ^[37].
11
- 12 ● Balance function will be measured by the Berg Balance Scale (BBS), which
13 consists of a set of 14 tasks to quantitatively assess the static and dynamic balance
14 abilities ^[38]. The BBS is not only one of the most important measurement scales to
15 evaluate the balance function of patients after stroke but can also be used as the risk
16 predictor of accidental fall in stroke patients ^[39].
17
- 18 ● Activities of Daily Living (ADL) will be assessed using the Modified Barthel
19 Index (MBI), which is a widely used standard scale for assessing functional
20 disability in basic ADL. The MBI contains 10 projects with a total of 100 points,
21 and the higher the score means the better the daily life self-care ability ^[40].
22
- 23 ● Quality of life will be measured by the Medical Outcomes Study 36-Item
24 Short-Form Health Survey (SF-36), which is currently the most commonly used in
25 clinical evaluation of quality of life in the general population and patients. The
26 SF-36 consists of 36 items to assess eight health concepts, and each of them is
27 evaluated separately by the normalized scores from 0 to 100, with the higher score
28 corresponding to better health status ^[41]. The Chinese SF-36 has been demonstrated
29 to have high reliability and validity in the Chinese population ^[42].
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Safety evaluation

Although no adverse events are reported currently regarding Baduanjin exercise, any unexpected adverse events during the intervention period will be reported to the research assistants, and causality in relation to the Baduanjin exercise training and the severity of adverse events will be evaluated. Serious adverse events will be reported to the ethics committee immediately.

Data management and monitoring

Data will be collected by the outcomes assessors using the print-based case report forms (p-CRFs), and the p-CRFs will later be inputted into the web-based case report forms (w-CRFs) in an electronic data capture system (EDC) by research assistants. The research assistants are also responsible for the integrity and accuracy of data when data are inputted into w-CRFs by means of checking on value ranges, or logical checks. The EDC system and web servers will be provided to the data management centre of FJTCM (<http://210.34.74.191/srtp/users/loginlength.action>) and meet the available standards for security (the data management centre, which belongs to the Science and Technology Department of FJTCM, is in charge of the monitoring and auditing of all research data in FJTCM). Participants' data in w-CRFs will be stored in the EDC system in a separate password-protected location. All documents will be retained securely for five years after completion of the study.

Statistical analysis

Statistical analysis will be performed using SPSS 22.0 (IBM, Chicago, IL, USA) software package by an independent statistician who is not involved in the outcome assessment, with a two-sided p value <0.05 being considered to be statistically

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3 significant. Continuous variables will be expressed using mean and its standard error
4 for normal distributions or median and its interquartile range for non-normal
5 distributions. Categorical variables will be described as frequencies or percentages.
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10 Baseline characteristics between comparison groups will be compared using a t-test or
11 Mann-Whitney U test for continuous variables and Pearson χ^2 or Fisher's exact test for
12 categorical variables.
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17 The analysis of primary or secondary outcomes will be based on an intention to treat
18 (ITT) principle, and the missing data will be imputed using a multiple imputation
19 method. The group difference between intervention and control group at each time
20 point (8-week, 16-week, and 24-week after intervention or 4-week follow-up period)
21 will be analysed using Student's t-test or Mann-Whitney U-test. Linear models or
22 linear regression will be applied to adjust analysis if incomparability of baseline
23 characteristics between groups appears. The linear mixed model with restricted
24 maximum likelihood will be used to analyse the interaction effect of Group \times Time.
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30 Adverse events (AEs) will be analysed using a chi-square test or Fisher's exact test. If
31 the formal statistical analyses between-groups cannot be performed due to the lack of
32 power, AEs will be tabulated and summarized using descriptive statistics.
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36 37 38 39 40 41 42 **Ethics**

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45 This study protocol conformed to the Declaration of Helsinki. Ethics approval of this
46 study protocol, and consent forms were obtained from the Ethics Committee of Fujian
47 University of Traditional Chinese Medicine Subsidiary Rehabilitation Hospital
48 (approval number: 2016KY-022-01). The study background and main objective as
49 well as potential benefits and risks will be fully explained to the participants and their
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3 families. Before participating in the study, participants will sign the informed consent
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5 document prior to participation.
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7 8 **Dissemination**

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10 The study protocol has been registered and is available on the Chinese Clinical Trial
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12 Registry website (<http://www.chictr.org.cn> with the identifier number ChiCTR-INR-
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14 16009364). Study results will be first informed to each participant and later
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16 disseminated to researchers, healthcare providers, healthcare professionals and the
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18 general public through courses, presentations and the internet, regardless of the
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20 magnitude or direction of effect. The results will also be documented in a published
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22 peer reviewed academic journal.
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26 27 **Discussion**

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29 As one of the most common forms of Chinese traditional exercises, Baduanjin
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31 exercise consists of eight separate movements, each of which focuses on a different
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33 physical area of the body ^[13]. Compared with other aerobic exercises, Baduanjin
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35 exercise is not only easy to learn but also is less physical and cognitive demanding ^[43].
36
37 Therefore, Baduanjin has become a popular and safe community exercise to promote
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39 health in the community of the older population of China. Furthermore, different from
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41 other types of aerobic exercise, Baduanjin is also a mind-body exercise combined
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43 with the holistic view and the theory of traditional Chinese medicine in that
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45 practitioners are required to reach coordination between mind and body ^[14]. Several
46
47 studies have reported that regular Baduanjin training has a positive effect in slowing
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49 normal age-related memory decline ^[20-21]. Zhu et al. even reported that Baduanjin
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51 exercise can delay the cognitive impairment progression for the elderly diabetic
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3 patients with mild cognitive impairment ^[44]. Therefore, it is reasonable to assume that
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5 regular Baduanjin training could be beneficial to cognitive function in stroke patients.
6
7 This proposed study aims to investigate the effect of Baduanjin exercise on cognitive
8
9 function, as well as observing the effect on motor function and quality of life in the
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11 stroke patients with cognitive impairment. This study will employ rigorousness to
12
13 control bias, such as randomization, parallel control, and blinding of the outcome
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15 assessors and statistician. To ensure participants master standard Baduanjin
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17 movements, we will also employ qualified physical exercise teachers to serve as the
18
19 Baduanjin exercise coaches. However, a potential limitation of this study is that
20
21 participants and coaches cannot be blinded because it is impossible to make them
22
23 blinded in non-pharmacological trials ^[45]. Therefore, performance bias may be
24
25 inevitable, but the exercise coaches will be not involved in the recruitment, outcome
26
27 assessment, or data analysis of this study. Another challenge that we may encounter
28
29 for the study is the difficulty in recruiting the eligible stroke patients. Those stroke
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31 patients or their families may worry about the exercise risk and prefer to stay in their
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33 home and maintain a fairly static life. In addition, a higher dropout rate may also be
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35 expected due to the above concerns. To address these problems, we will encourage
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37 participants to practice the Baduanjin training at their home after they master this
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39 exercise. We also accounted for the higher dropout rate in the sample size estimation
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41 to ensure the sufficient statistical power for the study.
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46
47 In summary, this report describes the first randomized controlled trial to evaluate
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49 systematically the rehabilitative effect of Baduanjin exercise on cognitive ability and
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51 motor function in stroke patients. This study will determine if Baduanjin training is
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53 likely to be effective in improving cognitive function, including global cognitive
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3 function and specific cognitive domains, in stroke patients with cognitive impairment.
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5 This study will also investigate if Baduanjin training can improve the motor function
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7 and quality of life for stroke patients with cognitive impairment and determine if this
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9 exercise is acceptable to them. If this trial is successfully conducted and demonstrates
10
11 a significant result, that intervention would provide an effective rehabilitation
12
13 approach for stroke patients and adequate supporting evidence for the application of
14
15 regular Baduanjin exercise in patients with post-stroke cognitive impairment.
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17 Conversely, if this exercise training is not effective, the study will identify the factors
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19 that contributed to the negative outcome.
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25 **Trial status**

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28 This trial is currently in the recruitment phase.
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35 **Abbreviations**

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38 SD: Standard deviation; DSM-V: Diagnostic and statistical manual disorders, 5th
39
40 edition; SAS 9.0: Statistical analysis system; TCM: Traditional Chinese medicine;
41
42 MoCA: Montreal cognitive assessment scale; FJTCM: Fujian University of
43
44 Traditional Chinese Medicine; TMT: Trail Making Test; AVLT: Auditory verbal
45
46 learning test; TAP: Test of attention performance; DSC: Digit symbol coding;
47
48 WAIS-RC: Wechsler adult intelligence scale-revised China; CDT: Clock drawing task;
49
50 FMA: Fugl-Meyer assessment scale; BBS: Berg balance scale; BI: Barthel index;
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55 ADL: Activities of daily living; SF-36: Item short-form health survey; CRF: Case
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4 report form; EDC: Electronic data capture system; SPSS 22.0: Statistic package for
5
6 social science 22.0; ITT: Intention to treat.
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9

11 **Declarations**

12
13
14 ZGH and ZYH contributed equally to this paper.
15

17 **Contributor ship statement**

18
19
20 CLD(Correspondence) and ZGH conceived and designed of the study protocol and
21
22 contributed to drafting the manuscript. ZYH and XZY wrote the manuscript and
23
24 participated in the coordination and implementation of the study. ZGH revised the
25
26 study protocol and wrote several sections of the manuscript. YBZ and TJ helped
27
28 develop the study measures and data collection. All authors contributed to drafting the
29
30 manuscript and have read and approved the final version of the manuscript.
31
32

33 **Funding**

34
35
36 This study is financially supported by the Shanghai Municipal Commission of Health
37
38 and Family Planning (No. 201640127) and the Specialized Research Fund for the Key
39
40 Disciplines of Fujian University of Traditional Chinese Medicine
41
42 (X2014070-Disciplines).
43
44

45 **Availability of data and materials**

46
47
48 This is not applicable because this is a paper of a study protocol.
49
50

51 **Consent for publication**

52
53
54 Not applicable.
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Competing interests

None declared.

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For peer review only

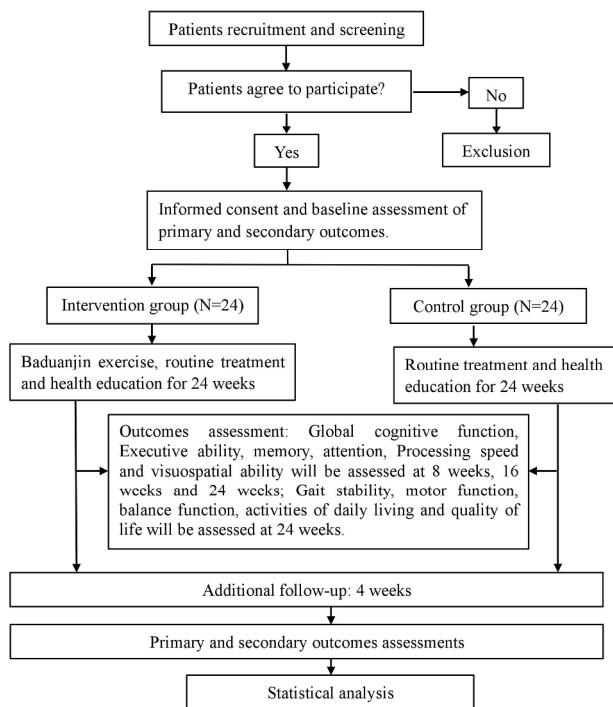


Figure 1 Flow diagram of study design

210x297mm (300 x 300 DPI)

STUDY PERIOD						
	Enrolment	Allocation	Intervention			Follow-up
TIMEPOINT*	- t_1	0	t_1	t_2	t_3	t_4
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
ALLOCATION						
		X				
INTERVENTIONS:						
Intervention group (Baduanjin exercise training+health education)			←————→			
Control group (Health education)			←————→			
ASSESSMENTS:						
Basic characteristics	X					
Global cognitive function	X		X	X	X	X
Executive ability	X		X	X	X	X
Memory	X		X	X	X	X
Attention	X		X	X	X	X
Processing speed	X		X	X	X	X
Visuospatial ability	X		X	X	X	X
Gait stability	X				X	X
Motor Function	X				X	X
Balance Function	X				X	X
Activities of Daily Living	X				X	X
Quality of Life	X				X	X
Adverse events			X	X	X	

<Figure Legend>

* - t_1 = -2(-1) weeks, 0 = Baseline, t_1 = Week 8, t_2 = Week 16, t_3 = End of treatment Week 24, t_4 = Follow Up Week 28.

Figure 2: Schedule of enrolment, interventions, and assessments

215x279mm (300 x 300 DPI)

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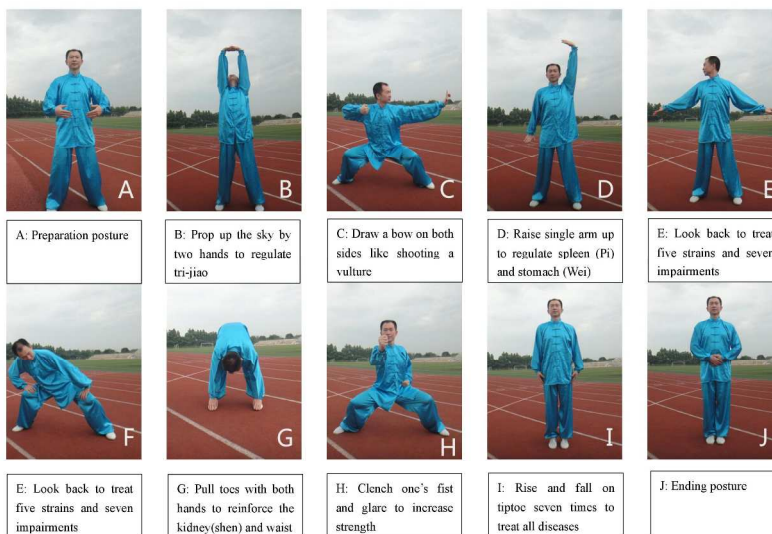


Figure 3: Ten postures of Baduanjin

297x210mm (300 x 300 DPI)



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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 21
	5b	Name and contact information for the trial sponsor	21
	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	21
	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)	18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	11
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			

1	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	8
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4	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)	7-8
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8	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
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11		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)	11
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14		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
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18		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-11
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21	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	13-16
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27	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)	Figure2
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31	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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34	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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37	Methods: Assignment of interventions (for controlled trials)			
38	Allocation:			
39	Allocation:			
40	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	9
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47	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	9-10
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52	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
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55	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
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1		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
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5	Methods: Data collection, management, and analysis			
6	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	16
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14		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	12&16
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17	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	16
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22	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	17
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26		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
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29		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)	17
30				
31				
32	Methods: Monitoring			
33				
34	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	16-17
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40		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	9
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44	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	16
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47	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
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51	Ethics and dissemination			
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53	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18
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1	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)	18
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5	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
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8		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9 & 16
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11	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	16-18
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15	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
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18	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	16 & 18
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21	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	Available in the informed consent materials
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25	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	18
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31		31b	Authorship eligibility guidelines and any intended use of professional writers	18
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34		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
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36	Appendices			
37				
38	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available in Chinese version
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41	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	Not applicable
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