

BMJ Open

Integrative Medicine for Sub-acute Stroke Rehabilitation: Study Protocol for a Multicenter, Randomized, Controlled Trial

| | |
|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID: | bmjopen-2014-007080 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 04-Nov-2014 |
| Complete List of Authors: | Fang, Jianqiao; The Third Affiliated Hospital of Zhejiang Chinese Medical University, Department of Acupuncture; Zhejiang Chinese Medical University, The Third Clinical Medical College Chen, Lifang; The Third Affiliated Hospital of Zhejiang Chinese Medical University, Department of Acupuncture Chen, Luni; Zhejiang Chinese Medical University, The Third Clinical Medical College Wang, Chao; Zhejiang Chinese Medical University, The Third Clinical Medical College Keeler, Crystal; Five Branches University, Innovations to Wellness Ma, Ruijie; The Third Affiliated Hospital of Zhejiang Cheinses Medical University, Department of Acupuncture Xu, Shouyu; The Third Affiliated Hospital of Zhejiang Chinese Medical University, Department of Rehabilitation Shen, Laihua; Jiaying Hospital of Traditional Chinese Medicine, Department of Acupuncture & Encephalopathy Bao, Yehua; Hangzhou Hospital of Traditional Chinese Medicine, Department of Acupuncture & Rehabilitation Ji, Conghua; Zhejiang Provincial Hospital of Traditional Chinese Medicine, The Clinical Research Institute |
| Primary Subject Heading: | Complementary medicine |
| Secondary Subject Heading: | Complementary medicine |
| Keywords: | STROKE MEDICINE, COMPLEMENTARY MEDICINE, Rehabilitation medicine < INTERNAL MEDICINE |
| | |

SCHOLARONE™
Manuscripts

1
2
3
4 **Integrative Medicine for Sub-acute Stroke Rehabilitation: Study**
5
6 **Protocol for a Multicenter, Randomized, Controlled Trial**
7

8 Jianqiao Fang,^{1,2*} Lifang Chen,¹ Luni Chen,² Chao Wang,² Crystal Lynn Keeler,³
9
10 Ruijie Ma,¹ Shouyu Xu,⁴ Laihua Shen,⁵ Yehua Bao,⁶ Conghua Ji,⁷
11

12
13 Correspondence to

14 Professor Jianqiao Fang^{1,2*};
15 fangjianqiao7532@163.com
16

17
18 Lifang Chen¹
19 Email: clfang@163.com
20

21
22 Luni Chen²
23 Email: clnhz@126.com
24

25
26 Chao Wang²
27 wangchaozy1126@163.com
28

29
30 Crystal Lynn Keeler³
31 Email: Crystal.clk@gmail.com
32

33
34 Ruijie Ma¹
35 Email: maria7878@sina.com
36

37
38 Shouyu Xu⁴
39 Email: overnightjo@msn.com
40

41
42 Laihua Shen⁵
43 Email: slh86ly@163.com
44

45
46 Yehua Bao⁶
47 Email: byh@hz.cn
48

49
50 Conghua Ji⁷
51 Email: jchi_2005@163.com
52
53
54
55
56
57
58
59
60

ABSTRACT

Introduction: Many stroke patients receive integrative medicine in China, which includes the basic treatment of Western medicine and routine rehabilitation, in conjunction with acupuncture and Chinese medicine. The question whether integrative medicine is efficacious for stroke rehabilitation is still controversial and very little research currently exists on the integrated approach for this condition. Consequently, we will conduct a multicenter, randomized, controlled, assessor-blinded clinical trial to assess the effectiveness of integrative medicine on stroke rehabilitation.

Methods and analysis: 360 participants recruited from three large Chinese medical hospitals in Zhejiang Province will be randomly divided into the integrative medicine rehabilitation (IMR) group and the conventional rehabilitation (CR) group in a 1:1 ratio. Participants in IMR group will receive acupuncture and Chinese herbs in addition to basic western medicine and rehabilitation treatment. The CR group will not receive acupuncture and Chinese herbal medicine. The assessment data will be collected at baseline, 4 and 8 weeks post-randomization, and then at 12-weeks follow-up. The primary outcome assessment tool, the Modified Barthel Index (MBI), will be used to evaluate activities of daily living (ADL). The secondary outcomes will be measured by the National Institutes of Health Stroke Scale (NIHSS) for neurologic deficits, Fugl-Meyer Assessment (FMA) for motor dysfunction, and the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) for cognitive impairment. For emotional disorders, the Hamilton's Depression Scale (HAMD) and Self-Rating Depression Scale (SDS) will measure emotional state, and the incidence of adverse events (AEs) will also be observed.

Ethics and dissemination: Ethical approval was obtained from ethics committees of the Third Affiliated Hospital of Zhejiang Chinese Medical University, the Hangzhou Hospital of Traditional Chinese Medicine and the Jiaying Hospital of Traditional Chinese Medicine. The results will be disseminated in a peer-reviewed journal and presented at international congresses.

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

Trial registration: Chinese Clinical Trial Register: ChiCTR-TRC-12001972,
<http://www.chictr.org/usercenter/project/edit.aspx?proj=2561>

Keywords Integrative Medicine, Sub-acute Stroke, Study Protocol, Randomized
Controlled Trial

For peer review only

INTRODUCTION

Stroke is the second most common cause of death and leading cause of adult disability worldwide¹. The number of patients who die from stroke is more than three times that from coronary heart disease². Modern Western medicine in China undoubtedly occupies the dominant position in prevention and treatment of stroke. However, most patients with stroke are treated with one or more types of Traditional Chinese Medicine (TCM) in addition to Western medicine. The role of TCM should not be ignored³⁻⁵. With the development of integrative medicine, which was established in the 1980s, more and more stroke patients receive integrative medicine treatment nowadays. The main integrative treatment includes the standard Western medicine and rehabilitation for stroke, as well as acupuncture and (or) Chinese herbs⁶. Nevertheless, there is not yet enough evidence to show the effect of integrative medicine for stroke. More rigorously designed, large scale, multicenter randomized trials are necessary, to assess the effectiveness of integrative medicine on stroke rehabilitation⁷.

METHODS

Study design

The study is a clinical research design on integrated rehabilitation with traditional Chinese and Western medicine on sub-acute stage of stroke, in a multicenter, randomized, controlled, assessor-blinded clinical trial. Participants recruited from three large Chinese medical hospitals, will be randomly divided into two groups (IMR group and CR group) using Statistical Product and Service Solutions (SPSS) statistical package program (ver. 17.0, SPSS Inc., Chicago, IL, USA) software. The CR group will receive basic Western medical treatment and rehabilitation, which includes physical treatment, and/or cognitive training for cognitive impairment, and/or psychological counseling for emotional disorders, six days per week. The IMR group will be additionally given acupuncture (thirty minutes of acupuncture therapy daily for six days per week lasting eight weeks) and Chinese herbs (treatment based

on syndrome differentiation for once a day lasting eight weeks). The specific route diagram is presented in figure 1.

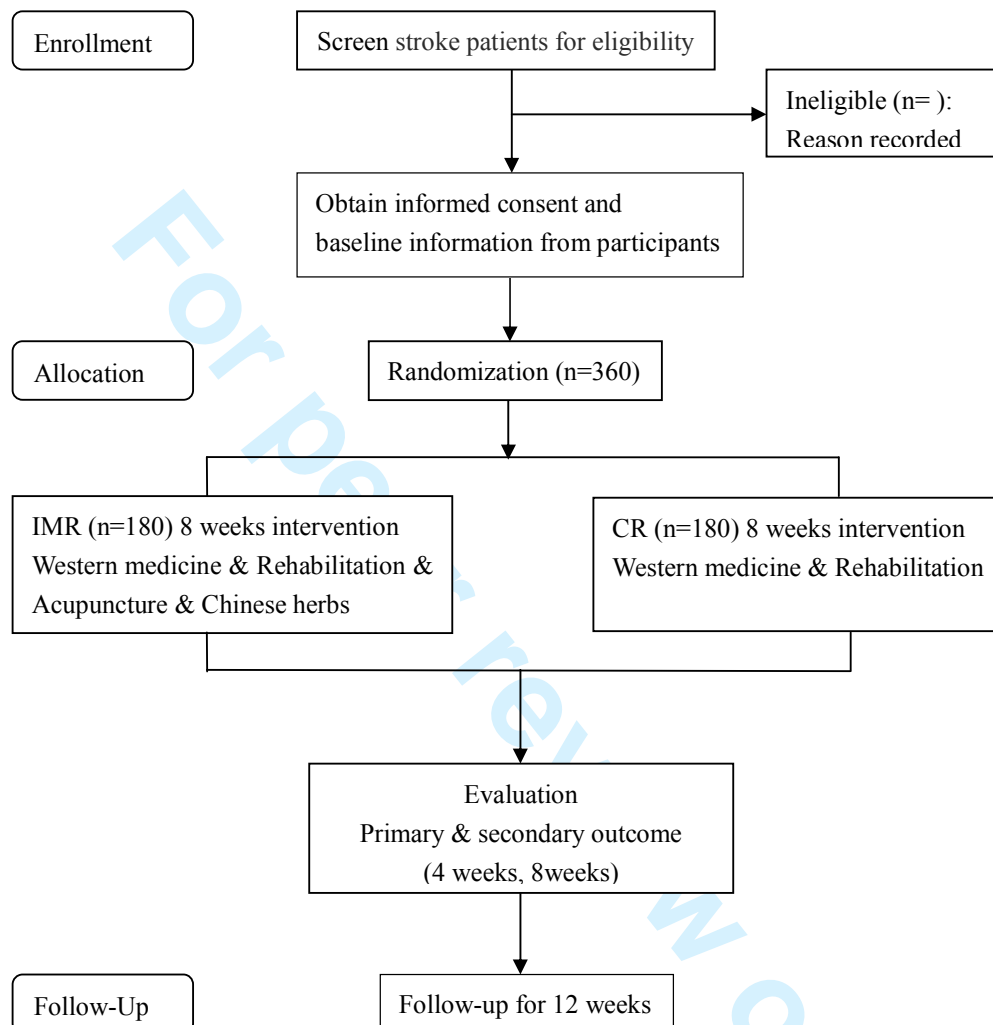


Figure 1. Route diagram of study design.

Participant recruitment

After getting the approval of Institutional Review Board, we recruited participants by advertising in local newspapers, health-related TV program, Internet and posters in hospitals and communities. The recruiting time was from March 1, 2012 to December 31, 2014. The patients intending to join the study can consult with study coordinators regarding any questions they may have. Once the patients qualified and agreed to participate in the study, informed consent was obtained prior to running the series of baseline measurement assessments.

Inclusion criteria

To be eligible, participants must meet the following conditions: (1) patients of 35-80 years old, with a recent (30~40 days) ischemic stroke; (2) patients with a NIHSS score of between 4 and 24; (3) The stroke should be the first incidence or patients can have a history of stroke, but without disability (modified Rankin Scale, mRS score ≤ 1).

Exclusion criteria

Participants who conform to any conditions below will be excluded: (1) Patients received thrombolytic therapy and participated in other clinical trials in last three months; (2) Patients who suffered from serious heart, liver, kidney related diseases, blood coagulation dysfunction, or severe mental disorders; (3) Patients who can not accept acupuncture, and(or) Chinese medicine treatment; (4) Women who are pregnant or breast-feeding.

Ethical considerations

Each of the ethics committees of the Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou Hospital of Traditional Chinese Medicine and Jiaying Hospital of Traditional Chinese Medicine, all approved the study. The purpose, nature, and potential risks of the experiments were fully explained to the patients and their families. All patients gave their written and oral informed consent before participating in the study.

Randomization and blinding

Randomization was done by computer software in the study. The generated random numbers was recorded in a small paper, which has been saved in sequentially numbered, opaque, sealed envelope. The envelopes were saved by the special screeners. When the participant is included, the screeners will open the envelope to get the group information. Then the subject was informed whether they will be in the treatment group or control group, with or without acupuncture & Chinese herbs. All of the rehabilitation therapists, outcome assessors, and data analysts are blinded to group assignments. However, it is impossible to make acupuncturists blinded, because they are trained to perform the treatment for participants of IMR group.

Interventions and comparison

The study is a randomized clinical trial carried out in three arms. Participants will be randomized to either the IMR group or CR group. Both groups will receive conventional stroke rehabilitation care, which includes normal limb posture, physiotherapy (PT) and occupational therapy (OT), and/or cognitive training for cognitive impairment, and/or psychological counseling for emotional disorder. The rehabilitation team develops the rehabilitation program according to the investigator's brochure. Rehabilitation includes physiotherapy and occupational therapy for two hours per day, six days per week for each participant. The IMR group will receive 30 additional minutes of acupuncture therapy every day, six days per week and take Chinese herbal decoction (twice a day) for eight weeks during the inpatient stay.

Acupuncture treatment

Acupuncture program is developed by experts of our project group, which has been discussed many times and performed by certified acupuncturists with more than five years of clinical experience. To ensure the same condition, all of the treatment protocols and processes will be written in detail as follows:

Scalp acupuncture: Select filiform needle (size 0.25 mm × 40 mm, Huatuo brand, manufactured by Suzhou Medical Appliance in Suzhou, Jiangsu Province China), swiftly insert the needle subcutaneously in 30° to the scalp on the top midline, the motor area and the sensory area of the affected side.

Body acupuncture (the affected side): LI15 (JianYu), LI11 (QuChi), LI10 (ShouSanLi), SJ5 (WaiGuan), LI4 (HeGu) for upper limbs; ST32 (BiGuan), St36 (ZuSanLi), GB34 (YangLingQuan), GB39 (XuanZhong), BL60 (KunLun) for lower limbs. Acupoints of the above are referred to the People's Republic of China, State Standard Name and Location of Acupoints (GB 12346-2006).

Modification according to dysfunction after stroke: For cognitive impairment patients, add GV20 (BaiHui), GV24 (ShenTing), GB13(BenShen), EX-HN1 (SiShenCong), Temple-Three-Needles (which is located in temple area, on the opposite side of hemiplegia, the first needle is located in 2 cun straight above ear apex, then the second and third needles are separately at the lateral 1 cun of the first needle).

1
2
3 For emotional disorder patients, add LR3 (TaiChong), PC6 (NeiGuan), GV20
4 (BaiHui), GV29 (Yin Tang), GV24 (Shen Ting).
5
6

7 Modification according to syndrome differentiation: For disturbance of wind-fire
8 type, add LR2 (Xing Jian), LR3 (Tai Chong), LR14(Qi Men); For phlegm-stasis
9 blocking collaterals, add SP10(Xue Hai), ST40(Feng Long); For yin deficiency and
10 wind act, add SP6 (San Yin Jiao), KI3(Tai Xi), LR3 (Tai Chong); For qi deficiency
11 and blood stasis type, add CV6(Qi Hai), CV4(Guan Yuan), BL17(Ge Shu).
12
13
14
15

16 Electro-acupuncture will be used when the patients De Qi (the sensation of
17 aching, numbness, tingling or warmth). Then, LI15 (Jian Yu) and LI11 (Qu Chi), St36
18 (Zu San Li) and GB39 (XuanZhong) will be connected to GB6805-2 Electro-Acu
19 Stimulators (Huayi Medical Supply & Equipment Co., Ltd, Shanghai, China). The
20 parameter is 2Hz intermittent wave at the intensity within patients' tolerance.
21
22
23

24 **Syndrome differentiation and Chinese herbal medicine**

25 The prescription of Chinese herbs is based on syndrome differentiation, we
26 formulated the treatment protocol through a systematic review, textbooks and ancient
27 literatures, as well as experts' experiences, and the final version of the protocol was
28 used for stroke patients of three centers before the trial carried out. There are four
29 types according to syndrome differentiation: (1)For the syndrome of disturbance of
30 wind-fire, Prescription: Tian Ma Gou Teng decoction modified (Tian Ma 9g, Gou
31 Teng 15g, Shi Jue Ming 15g, Shan Zhi Zi 9g, Huang Qin 9g, Chuan Niu Xi 15g, Du
32 Zhong 12g, Yi Mu Cao 15g, Sang Ji Sheng 15g, Ye Jiao Teng 9g, Fu Sheng 9g, raw
33 Long Gu 30g, raw Mu Li 30g); (2)For the syndrome of phlegm-stasis blocking
34 collaterals, Prescription: Ban Xia Bai Zhu Tian Ma decoction and Tao Hong Si Wu
35 decoction modified (Ban Xia 9g, Bai Zhu 9g, Tian Ma 9g, Fu Lin 9g, Ju Hong 6g,
36 Sheng Di 15g, Dang Gui 15g, Chuan Xiong 9g, Tao Ren 9g, Hong Hua 6g) (3)For the
37 syndrome of yin deficiency and wind act, Prescription: Zhen Gan Xi Feng decoction
38 modified (raw Long Gu 15g, raw Mu Li 15g, Dai Zhe Shi 30g, Gui Ban 15g, Bai
39 Shao 15g, Xuan Shen 15g, Tian Dong 15g, Chuan Lian Zi 6g, Yin Chen 6g, Chuan
40 Xiong 15g, raw Mai Ya 6g, fried Gan Cao 6g) (4)To syndrome of qi deficiency and
41 blood stasis, Prescription: Bu Yang Huan Wu decoction modified (raw Huang Qi 30g,
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Dang Gui 15g, Tao Ren 6g, Hong Hua 6g, Di Long 12g, Chi Shao 15g).

4 5 **Conventional Rehabilitation Group**

6
7 Patients in CR group do not receive acupuncture and Chinese herbs. This group only
8 receives basic Western medical and rehabilitation treatment, in the same frequency,
9 with the same course of treatment as the IMR group.
10

11 12 **Outcome assessment**

13
14 The assessment data will be collected at baseline, 4 and 8 weeks post-randomization,
15 and then 12 weeks after completing the treatment.
16

17 18 **Baseline assessment**

19
20 Demographic data includes gender, age, nationality, education level, occupation, and
21 marital status. Information on stroke risk factors regarding smoking, drinking, height,
22 weight, blood pressure, family history of stroke, blood lipids, and blood sugar is
23 gathered through review of the medical records. Several classifications of disease data
24 regarding: rehabilitation evaluation scales on neurological deficit, sensory motor,
25 cognitive, and emotional disorders will be also analyzed before randomization.
26
27

28 29 **Primary outcome measurement**

30
31 The primary outcome measurement is the Modified Barthel Index (MBI), which was
32 developed in 1955 as a simple index of independence useful in scoring disability⁸.
33 The MBI scale is a reliable measure of functional independence. It is sensitive and
34 valid to evaluate dependence in the activities of daily living (ADL). It includes ten
35 variables (defecating, urinating, feeding, bathing, grooming, dressing, toileting,
36 transfer, walking, and stairs) describing ADL and mobility. A higher number is
37 associated with a greater likelihood of being able to live at home with a degree of
38 independence. This index is used as a standardized assessment on rehabilitation wards
39 and also as standardized follow-up assessment to determine whether gains achieved
40 by patients with stroke while hospitalized are maintained after discharge⁹⁻¹¹.
41
42
43
44
45
46
47
48
49

50 51 **Secondary outcome measures**

52 53 **The National Institutes of Health Stroke Scale (NIHSS) for neurologic deficits**

54
55 The National Institutes of Health Stroke Scale (NIHSS) is a graded neurological
56 examination that assesses consciousness, best gaze, visual field, facial palsy, motor
57
58
59
60

1
2
3 arm, motor leg, limb ataxia, sensory, best language, dysphagia, and neglect. The scale
4 was developed for use in acute-stroke trials, and has since been widely used as a
5 standard part of the assessment in clinical trials. Its scores range is from 0 to 42, with
6 scores above 25 indicating very severe neurological impairment, scores of 5 to 24
7 suggesting moderately severe to severe impairment, and scores below 5 indicate mild
8 impairment¹²⁻¹³.

14 **The Fugl-Meyer Assessment (FMA) scale for motor dysfunction**

16 The FMA was developed as the first quantitative evaluative instrument for measuring
17 sensorimotor stroke recovery, which includes items dealing with the shoulder, elbow,
18 forearm, wrist, and hand in the upper extremity (UE, 66 points) and the hip, knee, and
19 ankle in the lower extremity (LE, 34 points)¹⁴. The motor domain has well-established
20 reliability and validity as an indicator of motor impairment severity across different
21 stroke recovery time points¹⁵.

28 **The Mini-Mental State Examination (MMSE) and Montreal Cognitive 29 Assessment (MoCA) for cognitive impairment**

31 Cognitive function is assessed by MMSE and MoCA scale. MMSE is a brief
32 wide-range screening test with 30 aggregate scores, which is more suitable for
33 uneducated or old populations. It assesses memory, orientation, calculation, attention,
34 expressing, and reading. In fact, MMSE is widely used because of its high specificity,
35 but it can't subtly detect mild cognitive impairment (MCI) patients, whose scores are
36 in the normal range¹⁶. In contrast, MoCA is more sensitive. It is also a test with 30
37 points, of which items including visual-spatial abilities, executive functions, attention,
38 concentration, memory, language, orientation. The MoCA detects MCI patients with
39 90% sensitivity and 87% specificity¹⁷.

48 **The Self-Rating Depression Scale (SDS) and Hamilton's Depression Scale 49 (HAMD) for emotional disorder**

52 SDS is a self-report instrument covering 20 items, either positive or negative, with a
53 four-point scale ranging from 1 to 4. The standardized score is the total score times
54 1.25, which results in 25 to 100¹⁸. Furthermore, in antidepressant clinical trials, the
55 Hamilton Depression Rating Scale has been the "gold standard" for use¹⁹. The
56
57
58
59
60

1
2
3 HAMD Scale we selected includes 24 items, consisting of sense of guilt, sleeping
4 problems, suicide, interest, anxiety, loss of weight, self-abasement, hopelessness, and
5 so on, 14 items with a score of 0-4 and 10 items with score of 0-2. The range of scores
6 for the whole test is 0-76. Higher scores indicate a higher level of mental disorder,
7 respectively²⁰.

12 **The incidence of adverse events**

13
14 Participants are to be questioned and report all adverse events (AEs) at each visit
15 point, and all AEs reports will be recorded and assessed by the investigators. If serious
16 adverse events happen, the researchers should report to the principal investigator and
17 ethics committee immediately, who will make a decision on whether the participant
18 needs to withdraw from the study.

19
20 In order to assess the safety of herbal medicine, we will perform the following
21 tests on participants of IMR group at the baseline (week 0) and after treatment (week
22 12): blood routine test, urine routine test, feces routine test, kidney function test, liver
23 function test. In addition, investigators will ask every subject at each visit whether
24 they have experienced allergies or gastrointestinal discomfort during the study period.

25
26 The adverse events of acupuncture may include local bleeding, hematoma, pallor,
27 sweating or dizziness, fainting during the acupuncture treatment, unbearable prickling,
28 retained needle after treatment. The investigator should record the date of occurrence,
29 time, degree, measurement related to the treatment, and consequence.

33 **Quality control and data management**

34
35 This is a 20-week clinical trial, in which participants need to take herbal medicine and
36 acupuncture for 8 weeks, and accept a 12-week follow-up, attend four assessment
37 visits (rehabilitation evaluation), obtain one set of laboratory tests (safety
38 assessments), Before the study, the trial protocol has been reviewed and revised by
39 experts on acupuncture, neurology, rehabilitation, statistics, and methodology several
40 times. All the members belonging to the trial are asked to take part in a series of
41 training to ensure that the personnel involved fully understand the research protocol
42 and standard operating procedures for the study. During the study, the Clinical
43 Research Institute of Zhejiang Provincial is responsible for quality control, and
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

censors have regular visits (once a month) to monitor protocol violations, the recruitment rate, AEs and participant compliance. A specified statistics centre will be responsible for data entering and management. All data will be double entered to ensure the accuracy and the source of any inconsistencies will be explored and resolved.

Sample size calculation

The primary efficacy parameter is the change in MBI scores from baseline to the end of treatment after eight weeks. Sample size calculations are based on our preliminary test and previous study²¹⁻²². The expected difference between CR group and IMR group is 10 value, it is to say the score of MBI of IMR group was 10 value higher than that of CR group, and the standard deviation is about 31. A two-sided 5% significance level and 80% power were considered, and the following equation was used:

$$n = \frac{2 \left(\frac{z_{\alpha/2} + z_{\beta}}{\Delta} \right)^2 \sigma^2}{\Delta^2}$$

Approximately 150 participants in each group were calculated to be required. Estimating a 20% dropout rate, each group will require 180 initial participants.

Statistical analysis

Efficacy and safety analyses will be conducted according to the intention-to-treat (ITT) principle by a statistician blinded to group allocation. Missing values will be imputed by the last-observation-carried-forward method. All statistical analyses will be performed using SPSS 17.0. The primary outcomes (MBI) and FMA will undergo ITT analysis including all the patients who are randomized. The analysis of cognitive impairment, emotional disorder will be made among the defined population of corresponding dysfunction. Continuous variables will be expressed as means with standard deviations. For normally distributed variables, two independent samples will be compared by t-test. On the other hand, for abnormally distributed variables, Non-parametric tests will be used, and the data will be expressed as medians with ranges. A P value of less than 0.05 is considered as statistical significance. Safety analysis is based on the frequency of adverse events relating to the treatment.

DISCUSSION

China's extensive experience in the use of traditional Chinese medicines in stroke therapy indicates that TCM preparations are effective, there are more than 100 traditional medicines in use for stroke therapy in China²³. But there was insufficient good quality evidence on the effects of TCM in ischemic stroke on the primary outcome²⁴. Or because of the significant clinical and methodological heterogeneity, no meta-analysis was performed and thus no cumulative result was obtained pooling data of RCTs²⁵. Further randomized controlled trials are justified.

Acupuncture is recommended for stroke according to the World Health Organization²⁶. However, reviews have shown that although acupuncture appeared to be safe, there is controversy of its benefit^{7, 27-28}.

Complementary or termed alternative medicine such as acupuncture and Chinese medicine, or integrative medicine has become increasingly prevalent and popular²⁹⁻³⁰. Integrated traditional Chinese and Western medicine for stroke rehabilitation is widely used in China. The integrated approach is forming some China characteristics of stroke treatment mode³¹. Many patients with stroke receive basic Western medicine and rehabilitation as well as acupuncture and Chinese medicine during hospital stays. So we conducted this clinical trial, which is close to the actual treatment strategy in China, to objectively evaluate the clinical efficacy. Syndrome differentiation and treatment is the essence of Chinese medicine, so in our study, Chinese herbal prescriptions for stroke patients are clarified. Four types of herbal medicine are most common in clinic according to syndrome differentiation. The acupuncture program traditionally includes scalp acupuncture and body acupuncture, and in addition some acupoints are selected according to the patient's dysfunction and also syndrome differentiation. Under strict quality control, this study could potentially confirm whether or not integrative medicine (IM) is an effective adjunct to the standard rehabilitation therapy for ischemic stroke. Our study may also assess the efficacy of IM in promoting the recovery of motor dysfunction, cognitive impairment and emotional disorder.

CONCLUSION

1
2
3 This trial has been designed to provide robust data on the efficacy of integrative
4 medicine for patients with ischemic stroke. It is also expected to clarify whether or
5 not integrative medicine is effective for motor, cognitive, or emotional disorder after
6 stroke.
7
8
9

10 11 **Trial status**

12 The trial is currently enrolling participants; recruitment started in March 1, 2012 and
13 will be completed in December 31, 2014.
14

15 16 **List of abbreviations used**

17 FMA, Fugl-Meyer Assessment; MCI, Mild Cognitive Impairment; MMSE,
18 Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NIHSS,
19 National Institutes of Health Stroke Scale; VFSS, Video-fluoroscopic Swallowing
20 Study; SPSS, Statistical Product and Service Solutions; mRS, modified Rankin Scale;
21 IMR, integrative medicine rehabilitation; CR, conventional rehabilitation; MBI,
22 Modified Barthel Index; ADL, activities of daily living; HAMD, Hamilton's
23 Depression Scale; SDS, Self-Rating Depression Scale; AEs, adverse events; TCM,
24 Traditional Chinese Medicine; PT, physiotherapy; OT, occupational therapy; IM,
25 integrative medicine.
26
27
28
29
30
31
32
33
34

35 36 **Competing interests**

37 The authors declare that they have no competing interests.
38

39 40 **Authors' contributions**

41 JQF, LFC, LNC, CW, CLK and CHJ and participated in the conception and design of
42 the trial, planning the analysis of the data and drafting the manuscript. RJM, SYX, LHS,
43 and YHB participated in data collection and are in charge of recruitment and treatment
44 of patients in each center. All the authors discussed, revised and approved the final
45 manuscript.
46
47
48
49

50 51 **Authors' information**

52 ¹ Department of Acupuncture, The Third Affiliated Hospital of Zhejiang Chinese
53 Medical University , No. 219 Moganshan Road, XiHu District, Hangzhou, Zhejiang
54 Province 310005, China
55
56
57
58
59
60

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

² The Third Clinical Medical College of Zhejiang Chinese Medical University , No. 548 Binwen Road, Binjiang District, Hangzhou, Zhejiang Province 310053, China

³ Innovations to Wellness. Affiliated with Five Branches University. 3031 Tisch Way, 5th floor Administration. San Jose, CA, 95128.

⁴ Department of Rehabilitation, The Third Affiliated Hospital of Zhejiang Chinese Medical University , No. 219 Moganshan Road, XiHu District, Hangzhou, Zhejiang Province 310005, China

⁵ Department of Acupuncture & Encephalopathy, Jiaying Hospital of Traditional Chinese Medicine. No. 1501 Zhongshan East Road, Jiaying, Zhejiang Province 310012, China

⁶ Department of Acupuncture & Rehabilitation, Hangzhou Hospital of Traditional Chinese Medicine. No. 453 Tiyuchang Road, XiHu District, Hangzhou, Zhejiang Province 310007, China

⁷ The Clinical Research Institute of Zhejiang Provincial Hospital of Traditional Chinese Medicine, No. 54 Youdian Road, Hangzhou, Zhejiang Province 310006, China

Acknowledgements and Funding

This study is funded by a project grant from the Provincial Administration of Traditional Chinese Medicine of Zhejiang (2011ZGG003). The team would like to thank three postgraduate students who contributed their time to the preliminary experiments (Pei Luo, Wei Dong, and Lu Zhang). We also appreciate the help and effort from the people participating in this trial.

References

1. Bonita R, Mendis S, Truelsen T, *et al.* The global stroke initiative. *The Lancet Neurology* 2004; 3(7):391–393.
2. Wang L, Kong L, Wu F, *et al.* Preventing chronic diseases in China. *The Lancet* 2005; 366(9499):1821–1824.
3. Liu M, Wu B, Wang WZ, *et al.* Stroke in China: epidemiology, prevention, and management strategies. *The Lancet Neurology* 2007; 6(5):456–464.
4. Liu L, Wang D, Wong KS, *et al.* Stroke and stroke care in China: huge burden, significant workload, and a national priority. *Stroke* 2011; 42:3651–3654.
5. Zhao D, Liu J, Wang W, *et al.* Epidemiological Transition of Stroke in China Twenty-One-Year Observational Study From the Sino-MONICA-Beijing Project. *Stroke* 2008; 39:1668–1674.
6. Wang J, Xiong X. Current situation and perspectives of clinical study in integrative medicine in China. *Evidence-Based Complementary and Alternative Medicine* 2012; 2012.
7. Wu HM, Tang JL, Lin XP, *et al.* Acupuncture for stroke rehabilitation. *Stroke* 2008; 39(2):517–518.
8. Mahoney FI. Functional evaluation: the Barthel index. *Maryland State Medical Journal* 1965; 14:61–65.
9. Collin C, Wade DT, Davies S, *et al.* The Barthel ADL Index: a reliability study. *Disability & Rehabilitation* 1988; 10(2):61–63.
10. Granger CV, Dewis LS, Peters NC, *et al.* Stroke rehabilitation: analysis of repeated Barthel index measures. *Archives of physical medicine and rehabilitation* 1979; 60(1):14–17.
11. Loewen SC, Anderson BA. Reliability of the modified motor assessment scale and the Barthel index. *Physical Therapy* 1988; 68(7):1077–1081.
12. Adams HP Jr, Davis PH, Leira EC, *et al.* Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* 1999; 53:126–131.

- 1
2
3 13. Goldstein LB, Samsa GP. Reliability of the National Institutes of Health Stroke Scale
4 extension to non-neurologists in the context of a clinical trial. *Stroke* 1997;
5 28(2):307–310.
6
7
- 8
9 14. Sanford J, Moreland J, Swanson LR, *et al.* Reliability of the Fugl-Meyer assessment
10 for testing motor performance in patients following stroke. *Physical therapy* 1993;
11 73(7):447–454.
12
13
- 14 15. Sullivan KJ, Tilson JK, Cen SY, *et al.* Fugl-Meyer assessment of sensorimotor
15 function after stroke: Standardized training procedure for clinical practice and clinical
16 trials. *Stroke* 2011; 42:427–432.
17
18
- 19 16. Smith T, Gildeh N, Holmes C. The Montreal Cognitive Assessment: validity and
20 utility in a memory clinic setting. *Canadian Journal of Psychiatry* 2007; 52(5):329.
21
22
- 23 17. Nasreddine ZS, Phillips NA, Bédirian V, *et al.* The Montreal Cognitive Assessment,
24 MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American*
25 *Geriatrics Society* 2005; 53(4):695–699.
26
27
- 28 18. Bose M, Shah P. Analyzing Post Stroke Depression (PSD) Levels in Stroke Patients
29 Using Zung Self-Rating Depression Scale. *Indian Journal of Physiotherapy and*
30 *Occupational Therapy-An International Journal* 2012; 6(4):187–190.
31
32
- 33 19. McIntyre RS, Konarski JZ, Mancini DA, *et al.* Measuring the severity of depression
34 and remission in primary care: validation of the HAMD–7 scale. *Canadian Medical*
35 *Association Journal* 2005;173(11):1327–1334.
36
37
- 38 20. Williams JBW, Kobak KA, Bech P, *et al.* The GRID-HAMD: standardization of the
39 Hamilton depression rating scale. *International clinical psychopharmacology* 2008;
40 23(3):120–129.
41
42
- 43 21. Gosman-Hedström G, Claesson L, Klingenstierna U, *et al.* Effects of acupuncture
44 treatment on daily life activities and quality of life a controlled, prospective, and
45 randomized study of acute stroke patients. *Stroke* 1998; 29(10):2100–2108.
46
47
- 48 22. Park J, White AR, James MA, *et al.* Acupuncture for subacute stroke rehabilitation: a
49 sham-controlled, subject-and assessor-blind, randomized trial. *Archives of internal*
50 *medicine* 2005; 165(17):2026–2031.
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
23. Gong X, Sucher NJ. Stroke therapy in traditional Chinese medicine (TCM): prospects for drug discovery and development. *Trends in pharmacological sciences* 1999; 20(5):191–196.
 24. Wu B, Liu M, Liu H, *et al.* Meta-analysis of traditional Chinese patent medicine for ischemic stroke. *Stroke* 2007; 38(6):1973–1979.
 25. Junhua Z, Menniti-Ippolito F, Xiumei G, *et al.* Complex traditional Chinese medicine for post stroke motor dysfunction a systematic review. *Stroke* 2009; 40(8):2797–2804.
 26. World Health Organization S: Acupuncture: Review and analysis of reports on controlled clinical trials. Geneva, Switzerland: *World Health Organization* 2003.
 27. Zhang SH, Liu M, Asplund K, *et al.* Acupuncture for acute stroke. *Stroke* 2005; 36:2327–2328.
 28. Sze FK, Wong E, Or KKH, *et al.* Does acupuncture improve motor recovery after stroke? A meta-analysis of randomized controlled trials. *Stroke* 2002; 33(11):2604–2619.
 29. Fontanarosa PB, Lundberg GD. Complementary, alternative, unconventional, and integrative medicine: call for papers for the annual coordinated theme issues of the AMA journals. *JAMA* 1997; 278(23):2111–2112.
 30. Maizes V, Rakel D, Niemiec C. Integrative medicine and patient-centered care. *Explore: The Journal of Science and Healing* 2009; 5(5):277–289.
 31. Wang J, Xiong X. Current situation and perspectives of clinical study in integrative medicine in China. *Evidence-Based Complementary and Alternative Medicine* 2012; 2012.

BMJ Open

Integrative Medicine for Sub-acute Stroke Rehabilitation: Study Protocol for a Multicenter, Randomized, Controlled Trial

| | |
|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID: | bmjopen-2014-007080.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 11-Nov-2014 |
| Complete List of Authors: | Fang, Jianqiao; The Third Affiliated Hospital of Zhejiang Chinese Medical University, Department of Acupuncture; Zhejiang Chinese Medical University, The Third Clinical Medical College Chen, Lifang; The Third Affiliated Hospital of Zhejiang Chinese Medical University, Department of Acupuncture Chen, Luni; Zhejiang Chinese Medical University, The Third Clinical Medical College Wang, Chao; Zhejiang Chinese Medical University, The Third Clinical Medical College Keeler, Crystal; Five Branches University, Innovations to Wellness Ma, Ruijie; The Third Affiliated Hospital of Zhejiang Cheinses Medical University, Department of Acupuncture Xu, Shouyu; The Third Affiliated Hospital of Zhejiang Chinese Medical University, Department of Rehabilitation Shen, Laihua; Jiaying Hospital of Traditional Chinese Medicine, Department of Acupuncture & Encephalopathy Bao, Yehua; Hangzhou Hospital of Traditional Chinese Medicine, Department of Acupuncture & Rehabilitation Ji, Conghua; Zhejiang Provincial Hospital of Traditional Chinese Medicine, The Clinical Research Institute |
| Primary Subject Heading: | Complementary medicine |
| Secondary Subject Heading: | Complementary medicine |
| Keywords: | STROKE MEDICINE, COMPLEMENTARY MEDICINE, Rehabilitation medicine < INTERNAL MEDICINE |
| | |

SCHOLARONE™
Manuscripts

Integrative Medicine for Sub-acute Stroke Rehabilitation: Study

Protocol for a Multicenter, Randomized, Controlled Trial

Jianqiao Fang,^{1,2*} Lifang Chen,¹ Luni Chen,² Chao Wang,² Crystal Lynn Keeler,³

Ruijie Ma,¹ Shouyu Xu,⁴ Laihua Shen,⁵ Yehua Bao,⁶ Conghua Ji,⁷

Correspondence to

Professor Jianqiao Fang^{1,2*};

fangjianqiao7532@163.com

Lifang Chen¹

Email: clfang@163.com

Luni Chen²

Email: clnhz@126.com

Chao Wang²

wangchaozy1126@163.com

Crystal Lynn Keeler³

Email: Crystal.clk@gmail.com

Ruijie Ma¹

Email: maria7878@sina.com

Shouyu Xu⁴

Email: overnightjo@msn.com

Laihua Shen⁵

Email: slh86ly@163.com

Yehua Bao⁶

Email: byh@hz.cn

Conghua Ji⁷

Email: jchi_2005@163.com

ABSTRACT

Introduction: Many stroke patients receive integrative medicine in China, which includes the basic treatment of Western medicine and routine rehabilitation, in conjunction with acupuncture and Chinese medicine. The question whether integrative medicine is efficacious for stroke rehabilitation is still controversial and very little research currently exists on the integrated approach for this condition. Consequently, we will conduct a multicenter, randomized, controlled, assessor-blinded clinical trial to assess the effectiveness of integrative medicine on stroke rehabilitation.

Methods and analysis: 360 participants recruited from three large Chinese medical hospitals in Zhejiang Province will be randomly divided into the integrative medicine rehabilitation (IMR) group and the conventional rehabilitation (CR) group in a 1:1 ratio. Participants in IMR group will receive acupuncture and Chinese herbs in addition to basic Western medicine and rehabilitation treatment. The CR group will not receive acupuncture and Chinese herbal medicine. The assessment data will be collected at baseline, 4 and 8 weeks post-randomization, and then at 12-weeks follow-up. The primary outcome assessment tool, the Modified Barthel Index (MBI), will be used to evaluate activities of daily living (ADL). The secondary outcomes will be measured by the National Institutes of Health Stroke Scale (NIHSS) for neurologic deficits, Fugl-Meyer Assessment (FMA) for motor dysfunction, and the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) for cognitive impairment. For emotional disorders, the Hamilton's Depression Scale (HAMD) and Self-Rating Depression Scale (SDS) will measure emotional state, and the incidence of adverse events (AEs) will also be observed.

Ethics and dissemination: Ethical approval was obtained from ethics committees of the Third Affiliated Hospital of Zhejiang Traditional Chinese Medical University, the Hangzhou Hospital of Traditional Chinese Medicine and the Jiaxing Hospital of Traditional Chinese Medicine. The results will be disseminated in a peer-reviewed journal and presented at international congresses. The results will also be

1
2
3 disseminated to patients by telephone, during follow-up calls inquiring on patient's
4 post-study health status.
5

6
7 **Trial registration:** Chinese Clinical Trial Register: ChiCTR-TRC-12001972,
8 <http://www.chictr.org/en/proj/show.aspx?proj=2561>
9

10
11
12
13 **Keywords** Integrative Medicine, Sub-acute Stroke, Study Protocol, Randomized
14 Controlled Trial
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

INTRODUCTION

Stroke is the second most common cause of death and leading cause of adult disability worldwide¹. The number of patients who die from stroke is more than three times that from coronary heart disease². Modern Western medicine in China undoubtedly occupies the dominant position in prevention and treatment of stroke. However, most patients with stroke are treated with one or more types of traditional Chinese medicine (TCM) in addition to Western medicine. The role of TCM should not be ignored³⁻⁵. With the development of integrative medicine, which was established in the 1980s, more and more stroke patients receive integrative medicine treatment. The main integrative treatment includes the standard Western medicine and rehabilitation for stroke, as well as acupuncture and (or) Chinese herbs⁶. Nevertheless, there is not yet enough evidence to show the effect of integrative medicine for stroke. More rigorously designed, large scale, multicenter randomized trials are necessary, to assess the effectiveness of integrative medicine on stroke rehabilitation⁷.

METHODS

Study design

The study is a clinical research design on integrated rehabilitation with traditional Chinese and Western medicine on sub-acute stage of stroke, in a multicenter, randomized, controlled, assessor-blinded clinical trial. Participants recruited from three large Chinese medical hospitals, will be randomly divided into two groups (IMR group and CR group) using Excel generated random numbers list. The CR group will receive basic Western medical treatment and rehabilitation, which includes physical therapy treatment, and/or cognitive training for cognitive impairment, and/or psychological counseling for emotional disorders, six days per week. The IMR group will be additionally given acupuncture (thirty minutes of acupuncture therapy daily for six days per week lasting eight weeks) and Chinese herbs (treatment based on syndrome differentiation for once a day lasting eight weeks). The specific route diagram is presented in figure 1.

Participant recruitment

After getting the approval of Institutional Review Board, we recruited participants by advertising in local newspapers, health-related TV programs, Internet and posters in hospitals and communities. The recruiting time was from March 1, 2012 to December 31, 2014. The patients intending to join the study can consult with study coordinators regarding any questions they may have. Once the patients qualified and agreed to participate in the study, informed consent was obtained prior to running the series of baseline measurement assessments.

Inclusion criteria

To be eligible, participants must meet the following conditions: (1) Patients 35-80 years old, with a recent (30~40 days) ischemic stroke; (2) Patients with a NIHSS score between 4 and 24; (3) The stroke should be the first incidence or patients can have a history of stroke, but without disability (modified Rankin Scale, mRS score ≤ 1).

Exclusion criteria

Participants who conform to any conditions below will be excluded: (1) Patients received thrombolytic therapy or participated in other clinical trials in last three months; (2) Patients who suffered from serious heart, liver, kidney related diseases, blood coagulation dysfunction, or severe mental disorders; (3) Patients who can not accept acupuncture, and(or) Chinese medicine treatment; (4) Women who are pregnant or breast-feeding; (5) patients with congenital disabilities.

Ethical considerations

Each of the ethics committees of the Third Affiliated Hospital of Zhejiang Traditional Chinese Medical University, Hangzhou Hospital of Traditional Chinese Medicine and Jiaxing Hospital of Traditional Chinese Medicine, all approved the study. The purpose, nature, and potential risks of the experiments were fully explained to the patients and their families. All patients gave their written and oral informed consent before participating in the study.

Randomization and blinding

Randomization was done by Excel computer software in the study. The generated list

1
2
3 of random numbers was printed, cut into small pieces, separated and placed into
4 sequentially numbered, opaque, sealed envelopes. The envelopes were saved by the
5 special screeners. When the participant is included, the screeners opened the envelope
6 to get the group information. Then the subject was informed whether they would be in
7 the treatment group or control group, with or without acupuncture & Chinese herbs.
8 All of the rehabilitation therapists, outcome assessors, and data analysts are blinded to
9 group assignments. However, it is impossible to make acupuncturists blinded, because
10 they are trained to perform the treatment for participants of IMR group.
11
12

13 **Interventions and comparison**

14
15 The study is a randomized clinical trial carried out in three centers. Participants will
16 be randomized to either the IMR group or CR group. Both groups will receive
17 conventional stroke rehabilitation care, which includes normal limb posture,
18 physiotherapy (PT) and occupational therapy (OT), and/or cognitive training for
19 cognitive impairment, and/or psychological counseling for emotional disorder. The
20 rehabilitation team develops the rehabilitation program according to the investigator's
21 brochure. Rehabilitation includes physiotherapy and occupational therapy for two
22 hours per day, six days per week for each participant. The IMR group will receive 30
23 additional minutes of acupuncture therapy every day, six days per week and take
24 Chinese herbal decoction (twice a day) for eight weeks during the inpatient stay.
25
26

27 **Acupuncture treatment**

28
29 The acupuncture program, developed by experts of our project group after many
30 discussions, was performed by certified acupuncturists with more than five years of
31 clinical experience. To ensure the same condition, all of the treatment protocols and
32 processes are detailed below:
33
34

35
36 Scalp acupuncture: Select filiform needle (size 0.25 mm × 40 mm, Huatuo brand,
37 manufactured by Suzhou Medical Appliance in Suzhou, Jiangsu Province China),
38 swiftly insert the needle subcutaneously in 30° to the scalp on the top midline, the
39 motor area and the sensory area of the affected side.
40
41

42
43 Body acupuncture (the affected side): LI15 (JianYu), LI11 (QuChi), LI10
44 (ShouSanLi), SJ5 (WaiGuan), LI4 (HeGu) for upper limbs; ST32 (BiGuan), ST36
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

(ZuSanLi), GB34 (YangLingQuan), GB39 (XuanZhong), BL60 (KunLun) for lower limbs. Acupoints of the above are referred to the People's Republic of China, State Standard Name and Location of Acupoints (GB 12346-2006).

Modification according to dysfunction after stroke: For cognitive impairment patients, add GV20 (BaiHui), GV24 (ShenTing), GB13 (BenShen), EX-HN1 (SiShenCong), Temple-Three-Needles (which is located in temple area, on the opposite side of hemiplegia, the first needle is located in 2 cun straight above ear apex, then the second and third needles are separately at the lateral 1 cun of the first needle). For emotional disorder patients, add LR3 (TaiChong), PC6 (NeiGuan), GV20 (BaiHui), GV29 (YinTang), GV24 (ShenTing).

Modification according to syndrome differentiation: For disturbance of wind-fire type, add LR2 (XingJian), LR3 (TaiChong), LR14 (QiMen); For phlegm-stasis blocking collaterals, add SP10 (XueHai), ST40 (FengLong); For yin deficiency and wind act, add SP6 (SanYinJiao), KI3 (TaiXi), LR3 (TaiChong); For qi deficiency and blood stasis type, add CV6 (QiHai), CV4 (GuanYuan), BL17 (GeShu).

Electro-acupuncture will be used when the patients De Qi (the sensation of aching, numbness, tingling or warmth). Then, LI15 (JianYu) and LI11 (QuChi), ST36 (ZuSanLi) and GB39 (XuanZhong) will be connected to GB6805-2 Electro-Acu Stimulators (Huayi Medical Supply & Equipment Co., Ltd, Shanghai, China). The parameter is 2Hz intermittent wave at the intensity within patients' tolerance.

Syndrome differentiation and Chinese herbal medicine

The prescription of Chinese herbs is based on syndrome differentiation. We formulated the treatment protocol through textbooks and ancient literatures, as well as experts' experiences, and the final version of the protocol was used for stroke patients of three centers before the trial carried out. There are four types according to syndrome differentiation: (1)For the syndrome of disturbance of wind-fire, Prescription: Tian Ma Gou Teng decoction modified (Tian Ma 9g, Gou Teng 15g, Shi Jue Ming 15g, Shan Zhi Zi 9g, Huang Qin 9g, Chuan Niu Xi 15g, Du Zhong 12g, Yi Mu Cao 15g, Sang Ji Sheng 15g, Ye Jiao Teng 9g, Fu Sheng 9g, raw Long Gu 30g, raw Mu Li 30g); (2)For the syndrome of phlegm-stasis blocking collaterals,

1
2
3 Prescription: Ban Xia Bai Zhu Tian Ma decoction and Tao Hong Si Wu decoction
4 modified (Ban Xia 9g, Bai Zhu 9g, Tian Ma 9g, Fu Lin 9g, Ju Hong 6g, Sheng Di 15g,
5 Dang Gui 15g, Chuan Xiong 9g, Tao Ren 9g, Hong Hua 6g) (3)For the syndrome of
6 yin deficiency and wind act, Prescription: Zhen Gan Xi Feng decoction modified (raw
7 Long Gu 15g, raw Mu Li 15g, Dai Zhe Shi 30g, Gui Ban 15g, Bai Shao 15g, Xuan
8 Shen 15g, Tian Dong 15g, Chuan Lian Zi 6g, Yin Chen 6g, Chuan Xiong 15g, raw
9 Mai Ya 6g, fried Gan Cao 6g) (4)For the syndrome of qi deficiency and blood stasis,
10 Prescription: Bu Yang Huan Wu decoction modified (raw Huang Qi 30g, Dang Gui
11 15g, Tao Ren 6g, Hong Hua 6g, Di Long 12g, Chi Shao 15g).
12
13
14
15
16
17
18
19

20 **Conventional Rehabilitation Group**

21 Patients in CR group do not receive acupuncture and Chinese herbs. This group only
22 receives basic Western medical and rehabilitation treatment, in the same frequency,
23 with the same course of treatment as the IMR group.
24
25
26
27

28 **Outcome assessment**

29 The assessment data will be collected at baseline, 4 and 8 weeks post-randomization,
30 and then 12 weeks after completing the treatment.
31
32

33 **Baseline assessment**

34 Demographic data includes gender, age, nationality, education level, occupation, and
35 marital status. Information on stroke risk factors regarding smoking, drinking, height,
36 weight, blood pressure, family history of stroke, blood lipids, and blood sugar is
37 gathered through review of the medical records. Several classifications of disease data
38 regarding: rehabilitation evaluation scales on neurological deficit, sensory motor,
39 cognitive, and emotional disorders will be also analyzed before randomization.
40
41
42
43
44
45
46

47 **Primary outcome measurement**

48 The primary outcome measurement is the Modified Barthel Index (MBI), which was
49 developed in 1955 as a simple index of independence useful in scoring disability⁸.
50 The MBI scale is a reliable measure of functional independence. It is sensitive and
51 valid to evaluate dependence in the activities of daily living (ADL). It includes ten
52 variables (defecating, urinating, feeding, bathing, grooming, dressing, toileting,
53 transfer, walking, and stairs) describing ADL and mobility. A higher number is
54
55
56
57
58
59
60

1
2
3 associated with a greater likelihood of being able to live at home with a degree of
4 independence. This index is used as a standardized assessment on rehabilitation wards
5 and also as standardized follow-up assessment to determine whether gains achieved
6 by patients with stroke while hospitalized are maintained after discharge⁹⁻¹¹.

11 **Secondary outcome measures**

12 **The National Institutes of Health Stroke Scale (NIHSS) for neurologic deficits**

13 The National Institutes of Health Stroke Scale (NIHSS) is a graded neurological
14 examination that assesses consciousness, best gaze, visual field, facial palsy, motor
15 arm, motor leg, limb ataxia, sensory, best language, dysphagia, and neglect. The scale
16 was developed for use in acute-stroke trials, and has since been widely used as a
17 standard part of the assessment in clinical trials. Its scores range is from 0 to 42, with
18 scores above 25 indicating very severe neurological impairment, scores of 5 to 24
19 suggesting moderately severe to severe impairment, and scores below 5 indicate mild
20 impairment¹²⁻¹³.

21 **The Fugl-Meyer Assessment (FMA) scale for motor dysfunction**

22 The FMA was developed as the first quantitative evaluative instrument for measuring
23 sensorimotor stroke recovery, which includes items dealing with the shoulder, elbow,
24 forearm, wrist, and hand in the upper extremity (UE, 66 points) and the hip, knee, and
25 ankle in the lower extremity (LE, 34 points)¹⁴. The motor domain has well-established
26 reliability and validity as an indicator of motor impairment severity across different
27 stroke recovery time points¹⁵.

28 **The Mini-Mental State Examination (MMSE) and Montreal Cognitive 29 Assessment (MoCA) for cognitive impairment**

30 Cognitive function is assessed by MMSE and MoCA scale. MMSE is a brief
31 wide-range screening test with 30 aggregate scores, which is more suitable for
32 uneducated or old populations. It assesses memory, orientation, calculation, attention,
33 expressing, and reading. In fact, MMSE is widely used because of its high specificity,
34 but it can't subtly detect mild cognitive impairment (MCI) patients, whose scores are
35 in the normal range¹⁶. In contrast, MoCA is more sensitive. It is also a test with 30
36 points, of which items including visual-spatial abilities, executive functions, attention,
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 concentration, memory, language, orientation. The MoCA detects MCI patients with
4 90% sensitivity and 87% specificity¹⁷.

5
6
7 **The Self-Rating Depression Scale (SDS) and Hamilton's Depression Scale**
8 **(HAMD) for emotional disorder**

9
10 SDS is a self-report instrument covering 20 items, either positive or negative, with a
11 four-point scale ranging from 1 to 4. The standardized score is the total score times
12 1.25, which results in 25 to 100¹⁸. Furthermore, in antidepressant clinical trials, the
13 Hamilton Depression Rating Scale has been the "gold standard" for use¹⁹. The
14 HAMD Scale we selected includes 24 items, consisting of sense of guilt, sleeping
15 problems, suicide, interest, anxiety, loss of weight, self-abasement, hopelessness, and
16 so on, 14 items with a score of 0-4 and 10 items with score of 0-2. The range of scores
17 for the whole test is 0-76. Higher scores indicate a higher level of mental disorder,
18 respectively²⁰.

19
20
21 **The incidence of adverse events**

22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
Participants are to be questioned and report all adverse events (AEs) at each visit
point, and all AEs reports will be recorded and assessed by the investigators. If serious
adverse events happen, the researchers should report to the principal investigator and
ethics committee immediately, who will make a decision on whether the participant
needs to withdraw from the study. If the participant suffered serious adverse events,
unbinding is permissible, and procedure is followed for revealing a participant's
allocated intervention during the trial. Compensation will be provided to those who
suffer harm from trial participation.

In order to assess the safety of herbal medicine, we will perform the following
tests on participants of IMR group at the baseline (week 0) and after treatment (week
12): blood routine test, urine routine test, feces routine test, kidney function test, liver
function test. In addition, investigators will ask every subject at each visit whether
they have experienced allergies or gastrointestinal discomfort during the study period.

The adverse events of acupuncture may include local bleeding, hematoma, pallor,
sweating or dizziness, fainting during the acupuncture treatment, unbearable prickling,
retained needle after treatment. The investigator should record the date of occurrence,

1
2
3 time, degree, measurement related to the treatment, and consequence.
4

5 **Quality control and data management**

6
7 This is a 20-week clinical trial, in which participants need to take herbal medicine and
8 acupuncture for 8 weeks, and accept a 12-week follow-up, attend four assessment
9 visits (rehabilitation evaluation), obtain one set of laboratory tests (safety
10 assessments), Before the study, the trial protocol has been reviewed and revised by
11 experts on acupuncture, neurology, rehabilitation, statistics, and methodology several
12 times. All the members belonging to the trial are asked to take part in a series of
13 training to ensure that the personnel involved fully understand the research protocol
14 and standard operating procedures for the study. During the study, the Clinical
15 Research Institute of Zhejiang Provincial is responsible for generating the allocation
16 sequence, quality control, and censors have regular visits (once a month) to monitor
17 protocol violations, the recruitment rate, AEs and participant compliance. This clinical
18 trial is independent from sponsors and competing interests. The clinical coordinators
19 of three centers are specifically designated to enroll participants, and assign
20 participants to interventions, but not to participate in treatment and assessment for
21 subjects. Outcome assessors and data analysts will be blinded after assignment to
22 interventions, without access to patients' group information.
23
24
25
26
27
28
29
30
31
32
33
34
35
36

37 The measurements are mainly rehabilitation evaluations. All of the data will first
38 be recorded on the paper version of the case report form (CRF) by assessors, then
39 double entered into EDC system electronically. A specified statistics centre of the
40 Clinical Research Institute of Zhejiang Province will responsible for data management.
41 All data will be double entered to ensure accuracy. The source of any inconsistencies
42 will be explored and resolved.
43
44
45
46
47

48 **Sample size calculation**

49
50 The primary efficacy parameter is the change in MBI scores from baseline to the end
51 of treatment after eight weeks. Sample size calculations are based on our preliminary
52 test and previous study²¹⁻²², The expected difference between CR group and IMR
53 group is 10 value, it is to say the score of MBI of IMR group was 10 value higher than
54
55
56
57
58
59
60

1
2
3 that of CR group, and the standard deviation is about 31, A two-sided 5% significance
4 level and 80% power were considered, and the following equation was used:
5
6

$$7 \quad n = \frac{2 \left(\frac{z_{\alpha}}{2} + z_{\beta} \right)^2 \sigma^2}{8 \quad \Delta^2}$$

9
10
11
12 Approximately 150 participants in each group were calculated to be required.
13
14 Estimating a 20% dropout rate, each group will require 180 initial participants.
15

16 **Statistical analysis**

17
18 Efficacy and safety analyses will be conducted according to the intention-to-treat (ITT)
19 principle by a statistician blinded to group allocation. Missing values will be imputed
20 by the last-observation-carried-forward method. All statistical analyses will be
21 performed using Statistical Product and Service Solutions (SPSS) statistical package
22 program (ver. 17.0, SPSS Inc., Chicago, IL, USA). The primary outcomes (MBI) and
23 FMA will undergo ITT analysis including all the patients who are randomized. The
24 analysis of cognitive impairment, emotional disorder will be made among the defined
25 population of corresponding dysfunction. Continuous variables will be expressed as
26 means with standard deviations. For normally distributed variables, two independent
27 samples will be compared by t-test. On the other hand, for abnormally distributed
28 variables, Non-parametric tests will be used, and the data will be expressed as
29 medians with ranges. A P-value of less than 0.05 is considered as statistical
30 significance. Safety analysis is based on the frequency of adverse events relating to
31 the treatment.
32
33
34
35
36
37
38
39
40
41
42
43

44 **DISCUSSION**

45
46 China's extensive clinical experience in the use of traditional Chinese medicines in
47 stroke therapy indicates that TCM preparations are effective. More than 100
48 traditional medicines are currently in use for stroke therapy in China²³. However,
49 insufficient good-quality evidence on the effects of TCM in ischemic stroke exists on
50 the primary outcome²⁴. One possibility for lack of evidence in the literature could
51 result from the significant clinical and methodological heterogeneity, preventing
52 effective meta-analysis techniques. No meta-analysis have been performed and thus
53
54
55
56
57
58
59
60

1
2
3 no cumulative results obtained by pooling RCT data exist²⁵. Further randomized
4 controlled trials are justified.
5

6 Acupuncture is recommended for stroke according to the World Health
7 Organization²⁶. Literature reviews have demonstrated the safety of acupuncture,
8 legitimizing its ethical use for patients, without causing harm⁷. Despite its safety, the
9 limited availability of rigorous RCTs and the lack of research available on
10 complementary and alternative medicine treatments like acupuncture, create a
11 controversial opinion on its benefit for specific disease outcomes^{7,27-28}. This lack of
12 evidence necessitates additional RCT study on the clinical efficacy of integrative
13 medicine on stroke outcomes.
14
15
16
17
18
19

20 Complementary or termed alternative medicine such as acupuncture and Chinese
21 medicine, or integrative medicine has become increasingly prevalent and popular, not
22 only in China, but also worldwide²⁹⁻³⁰. Integrated traditional Chinese and Western
23 medicine for stroke rehabilitation is widely used in China, making it an ideal setting
24 to study stroke treatment protocols. The integrated approach is forming some of China
25 characteristics of stroke treatment modalities, which can be observed as a model for
26 the rest of the world³¹. Many patients in China, with stroke, receive basic Western
27 medicine and rehabilitation as well as acupuncture and Chinese medicine during
28 hospital stays. So we are conducting this clinical trial, which is close to the actual
29 treatment strategy in China, to objectively evaluate the clinical efficacy. Syndrome
30 differentiation and treatment is the essence of Chinese medicine, so in our study,
31 Chinese herbal prescriptions for stroke patients are clarified. Four types of herbal
32 medicine are most common in clinic according to syndrome differentiation. The
33 acupuncture program traditionally includes scalp acupuncture and body acupuncture,
34 and in addition some acupoints are selected according to the patient's dysfunction and
35 also syndrome differentiation. Under strict quality control, this study could potentially
36 confirm whether or not integrative medicine (IM) is an effective adjunct to the
37 standard rehabilitation therapy for ischemic stroke. Our study may also assess the
38 efficacy of IM in promoting the recovery of motor dysfunction, cognitive impairment
39 and emotional disorder.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56

57 **CONCLUSION**

1
2
3 This trial has been designed to provide robust data on the efficacy of integrative
4 medicine for patients with ischemic stroke. It is also expected to clarify whether or
5 not integrative medicine is effective for motor, cognitive, or emotional disorder after
6 stroke.
7
8
9

10 11 **Trial status**

12 The trial is currently enrolling participants; recruitment started in March 1, 2012 and
13 will be completed in December 31, 2014.
14

15 16 **List of abbreviations used**

17 FMA, Fugl-Meyer Assessment; MCI, Mild Cognitive Impairment; MMSE,
18 Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NIHSS,
19 National Institutes of Health Stroke Scale; VFSS, Video-fluoroscopic Swallowing
20 Study; SPSS, Statistical Product and Service Solutions; mRS, modified Rankin Scale;
21 IMR, integrative medicine rehabilitation; CR, conventional rehabilitation; MBI,
22 Modified Barthel Index; ADL, activities of daily living; HAMD, Hamilton's
23 Depression Scale; SDS, Self-Rating Depression Scale; AEs, adverse events; TCM,
24 traditional Chinese medicine; PT, physiotherapy; OT, occupational therapy; IM,
25 integrative medicine.
26
27
28
29
30
31
32
33
34

35 36 **Competing interests**

37 The authors declare that they have no competing interests.
38

39 40 **Authors' contributions**

41 JQF, LFC, LNC, CW, CLK and CHJ and participated in the conception and design of
42 the trial, planning the analysis of the data and drafting the manuscript. RJM, SYX, LHS,
43 and YHB participated in data collection and are in charge of recruitment and treatment
44 of patients in each center. All the authors discussed, revised and approved the final
45 manuscript.
46
47
48
49

50 51 **Authors' information**

52 ¹ Department of Acupuncture, The Third Affiliated Hospital of Zhejiang Traditional
53 Chinese Medical University, No. 219 Moganshan Road, XiHu District, Hangzhou,
54 Zhejiang Province 310005, China
55
56
57
58
59
60

² The Third Clinical Medical College of Zhejiang Traditional Chinese Medical University, No. 548 Binwen Road, Binjiang District, Hangzhou, Zhejiang Province 310053, China

³ Innovations to Wellness. Affiliated with Five Branches University. 3031 Tisch Way, 5th floor Administration. San Jose, CA, 95128.

⁴ Department of Rehabilitation, The Third Affiliated Hospital of Zhejiang Traditional Chinese Medical University, No. 219 Moganshan Road, XiHu District, Hangzhou, Zhejiang Province 310005, China

⁵ Department of Acupuncture & Encephalopathy, Jiaying Hospital of Traditional Chinese Medicine. No. 1501 Zhongshan East Road, Jiaying, Zhejiang Province 310012, China

⁶ Department of Acupuncture & Rehabilitation, Hangzhou Hospital of Traditional Chinese Medicine. No. 453 Tiyuchang Road, XiHu District, Hangzhou, Zhejiang Province 310007, China

⁷ The Clinical Research Institute of Zhejiang Provincial Hospital of Traditional Chinese Medicine, No. 54 Youdian Road, Hangzhou, Zhejiang Province 310006, China

Acknowledgements and Funding

This study is funded by a project grant from the Provincial Administration of Traditional Chinese Medicine of Zhejiang (2011ZGG003), and the funder will not have a role in the conduction or interpretation of this trial, or in any decision to publish the results. The team would like to thank three postgraduate students who contributed their time to the preliminary experiments (Pei Luo, Wei Dong, and Lu Zhang). We also appreciate the help and effort from the people participating in this trial.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is

properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/3.0/>

References

1. Bonita R, Mendis S, Truelsen T, *et al.* The global stroke initiative. *The Lancet Neurology* 2004; 3(7):391–393.
2. Wang L, Kong L, Wu F, *et al.* Preventing chronic diseases in China. *The Lancet* 2005; 366(9499):1821–1824.
3. Liu M, Wu B, Wang WZ, *et al.* Stroke in China: epidemiology, prevention, and management strategies. *The Lancet Neurology* 2007; 6(5):456–464.
4. Liu L, Wang D, Wong KS, *et al.* Stroke and stroke care in China: huge burden, significant workload, and a national priority. *Stroke* 2011; 42:3651–3654.
5. Zhao D, Liu J, Wang W, *et al.* Epidemiological Transition of Stroke in China Twenty-One-Year Observational Study From the Sino-MONICA-Beijing Project. *Stroke* 2008; 39:1668–1674.
6. Wang J, Xiong X. Current situation and perspectives of clinical study in integrative medicine in China. *Evidence-Based Complementary and Alternative Medicine* 2012; 2012.
7. Wu HM, Tang JL, Lin XP, *et al.* Acupuncture for stroke rehabilitation. *Stroke* 2008; 39(2):517–518.
8. Mahoney FI. Functional evaluation: the Barthel index. *Maryland State Medical Journal* 1965; 14:61–65.
9. Collin C, Wade DT, Davies S, *et al.* The Barthel ADL Index: a reliability study. *Disability & Rehabilitation* 1988; 10(2):61–63.
10. Granger CV, Dewis LS, Peters NC, *et al.* Stroke rehabilitation: analysis of repeated Barthel index measures. *Archives of physical medicine and rehabilitation* 1979; 60(1):14–17.
11. Loewen SC, Anderson BA. Reliability of the modified motor assessment scale and the Barthel index. *Physical Therapy* 1988; 68(7):1077–1081.
12. Adams HP Jr, Davis PH, Leira EC, *et al.* Baseline NIH Stroke Scale score strongly

- 1
2
3 predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke
4 Treatment (TOAST). *Neurology* 1999; 53:126–131.
- 5
6 13. Goldstein LB, Samsa GP. Reliability of the National Institutes of Health Stroke Scale
7 extension to non-neurologists in the context of a clinical trial. *Stroke* 1997;
8 28(2):307–310.
- 9
10 14. Sanford J, Moreland J, Swanson LR, *et al.* Reliability of the Fugl-Meyer assessment
11 for testing motor performance in patients following stroke. *Physical therapy* 1993;
12 73(7):447–454.
- 13
14 15. Sullivan KJ, Tilson JK, Cen SY, *et al.* Fugl-Meyer assessment of sensorimotor
15 function after stroke: Standardized training procedure for clinical practice and clinical
16 trials. *Stroke* 2011; 42:427–432.
- 17
18 16. Wind AW, Schellevis FG, Van Staveren G, *et al.* Limitations of the Mini-Mental
19 State Examination in diagnosing dementia in general practice[J]. *International journal*
20 *of geriatric psychiatry* 1997;12(1): 101-108.
- 21
22 17. Nasreddine ZS, Phillips NA, Bédirian V, *et al.* The Montreal Cognitive Assessment,
23 MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American*
24 *Geriatrics Society* 2005; 53(4):695–699.
- 25
26 18. Bose M, Shah P. Analyzing Post Stroke Depression (PSD) Levels in Stroke Patients
27 Using Zung Self-Rating Depression Scale. *Indian Journal of Physiotherapy and*
28 *Occupational Therapy-An International Journal* 2012; 6(4):187–190.
- 29
30 19. McIntyre RS, Konarski JZ, Mancini DA, *et al.* Measuring the severity of depression
31 and remission in primary care: validation of the HAMD–7 scale. *Canadian Medical*
32 *Association Journal* 2005;173(11):1327–1334.
- 33
34 20. Williams JBW, Kobak KA, Bech P, *et al.* The GRID-HAMD: standardization of the
35 Hamilton depression rating scale. *International clinical psychopharmacology* 2008;
36 23(3):120–129.
- 37
38 21. Gosman-Hedström G, Claesson L, Klingenstierna U, *et al.* Effects of acupuncture
39 treatment on daily life activities and quality of life a controlled, prospective, and
40 randomized study of acute stroke patients. *Stroke* 1998; 29(10):2100–2108.
- 41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
22. Park J, White AR, James MA, *et al.* Acupuncture for subacute stroke rehabilitation: a sham-controlled, subject-and assessor-blind, randomized trial. *Archives of internal medicine* 2005; 165(17):2026–2031.
 23. Gong X, Sucher NJ. Stroke therapy in traditional Chinese medicine (TCM): prospects for drug discovery and development. *Trends in pharmacological sciences* 1999; 20(5):191–196.
 24. Wu B, Liu M, Liu H, *et al.* Meta-analysis of traditional Chinese patent medicine for ischemic stroke. *Stroke* 2007; 38(6):1973–1979.
 25. Junhua Z, Menniti-Ippolito F, Xiumei G, *et al.* Complex traditional Chinese medicine for post stroke motor dysfunction a systematic review. *Stroke* 2009; 40(8):2797–2804.
 26. World Health Organization S: Acupuncture: Review and analysis of reports on controlled clinical trials. Geneva, Switzerland: *World Health Organization* 2003.
 27. Zhang SH, Liu M, Asplund K, *et al.* Acupuncture for acute stroke. *Stroke* 2005; 36:2327–2328.
 28. Sze FK, Wong E, Or KKH, *et al.* Does acupuncture improve motor recovery after stroke? A meta-analysis of randomized controlled trials. *Stroke* 2002; 33(11):2604–2619.
 29. Fontanarosa PB, Lundberg GD. Complementary, alternative, unconventional, and integrative medicine: call for papers for the annual coordinated theme issues of the AMA journals. *JAMA* 1997; 278(23):2111–2112.
 30. Maizes V, Rakel D, Niemiec C. Integrative medicine and patient-centered care. *Explore: The Journal of Science and Healing* 2009; 5(5):277–289.
 31. Wang J, Xiong X. Current situation and perspectives of clinical study in integrative medicine in China. *Evidence-Based Complementary and Alternative Medicine* 2012; 2012.

Integrative Medicine for Sub-acute Stroke Rehabilitation: Study

Protocol for a Multicenter, Randomized, Controlled Trial

Jianqiao Fang,^{1,2*} Lifang Chen,¹ Luni Chen,² Chao Wang,² Crystal Lynn Keeler,³

Ruijie Ma,¹ Shouyu Xu,⁴ Laihua Shen,⁵ Yehua Bao,⁶ Conghua Ji,⁷

Correspondence to

Professor Jianqiao Fang^{1,2*};

fangjianqiao7532@163.com

Lifang Chen¹

Email: clfang@163.com

Luni Chen²

Email: clnhz@126.com

Chao Wang²

wangchaozy1126@163.com

Crystal Lynn Keeler³

Email: Crystal.clk@gmail.com

Ruijie Ma¹

Email: maria7878@sina.com

Shouyu Xu⁴

Email: overnightjo@msn.com

Laihua Shen⁵

Email: slh86ly@163.com

Yehua Bao⁶

Email: byh@hz.cn

Conghua Ji⁷

Email: jchi_2005@163.com

ABSTRACT

Introduction: Many stroke patients receive integrative medicine in China, which includes the basic treatment of Western medicine and routine rehabilitation, in conjunction with acupuncture and Chinese medicine. The question whether integrative medicine is efficacious for stroke rehabilitation is still controversial and very little research currently exists on the integrated approach for this condition. Consequently, we will conduct a multicenter, randomized, controlled, assessor-blinded clinical trial to assess the effectiveness of integrative medicine on stroke rehabilitation.

Methods and analysis: 360 participants recruited from three large Chinese medical hospitals in Zhejiang Province will be randomly divided into the integrative medicine rehabilitation (IMR) group and the conventional rehabilitation (CR) group in a 1:1 ratio. Participants in IMR group will receive acupuncture and Chinese herbs in addition to basic Western medicine and rehabilitation treatment. The CR group will not receive acupuncture and Chinese herbal medicine. The assessment data will be collected at baseline, 4 and 8 weeks post-randomization, and then at 12-weeks follow-up. The primary outcome assessment tool, the Modified Barthel Index (MBI), will be used to evaluate activities of daily living (ADL). The secondary outcomes will be measured by the National Institutes of Health Stroke Scale (NIHSS) for neurologic deficits, Fugl-Meyer Assessment (FMA) for motor dysfunction, and the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) for cognitive impairment. For emotional disorders, the Hamilton's Depression Scale (HAMD) and Self-Rating Depression Scale (SDS) will measure emotional state, and the incidence of adverse events (AEs) will also be observed.

Ethics and dissemination: Ethical approval was obtained from ethics committees of the Third Affiliated Hospital of Zhejiang Traditional Chinese Medical University, the Hangzhou Hospital of Traditional Chinese Medicine and the Jiaxing Hospital of Traditional Chinese Medicine. The results will be disseminated in a peer-reviewed journal and presented at international congresses. The results will also be

1
2
3 disseminated to patients by telephone, during follow-up calls inquiring on patient's
4
5 post-study health status.
6

7 **Trial registration:** Chinese Clinical Trial Register: ChiCTR-TRC-12001972,
8
9 <http://www.chictr.org/en/proj/show.aspx?proj=2561>
10

11
12
13 **Keywords** Integrative Medicine, Sub-acute Stroke, Study Protocol, Randomized
14
15 Controlled Trial
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

INTRODUCTION

Stroke is the second most common cause of death and leading cause of adult disability worldwide¹. The number of patients who die from stroke is more than three times that from coronary heart disease². Modern Western medicine in China undoubtedly occupies the dominant position in prevention and treatment of stroke. However, most patients with stroke are treated with one or more types of traditional Chinese medicine (TCM) in addition to Western medicine. The role of TCM should not be ignored³⁻⁵. With the development of integrative medicine, which was established in the 1980s, more and more stroke patients receive integrative medicine treatment. The main integrative treatment includes the standard Western medicine and rehabilitation for stroke, as well as acupuncture and (or) Chinese herbs⁶. Nevertheless, there is not yet enough evidence to show the effect of integrative medicine for stroke. More rigorously designed, large scale, multicenter randomized trials are necessary, to assess the effectiveness of integrative medicine on stroke rehabilitation⁷.

METHODS

Study design

The study is a clinical research design on integrated rehabilitation with traditional Chinese and Western medicine on sub-acute stage of stroke, in a multicenter, randomized, controlled, assessor-blinded clinical trial. Participants recruited from three large Chinese medical hospitals, will be randomly divided into two groups (IMR group and CR group) using Excel generated random numbers list. The CR group will receive basic Western medical treatment and rehabilitation, which includes physical therapy treatment, and/or cognitive training for cognitive impairment, and/or psychological counseling for emotional disorders, six days per week. The IMR group will be additionally given acupuncture (thirty minutes of acupuncture therapy daily for six days per week lasting eight weeks) and Chinese herbs (treatment based on syndrome differentiation for once a day lasting eight weeks). The specific route diagram is presented in figure 1.

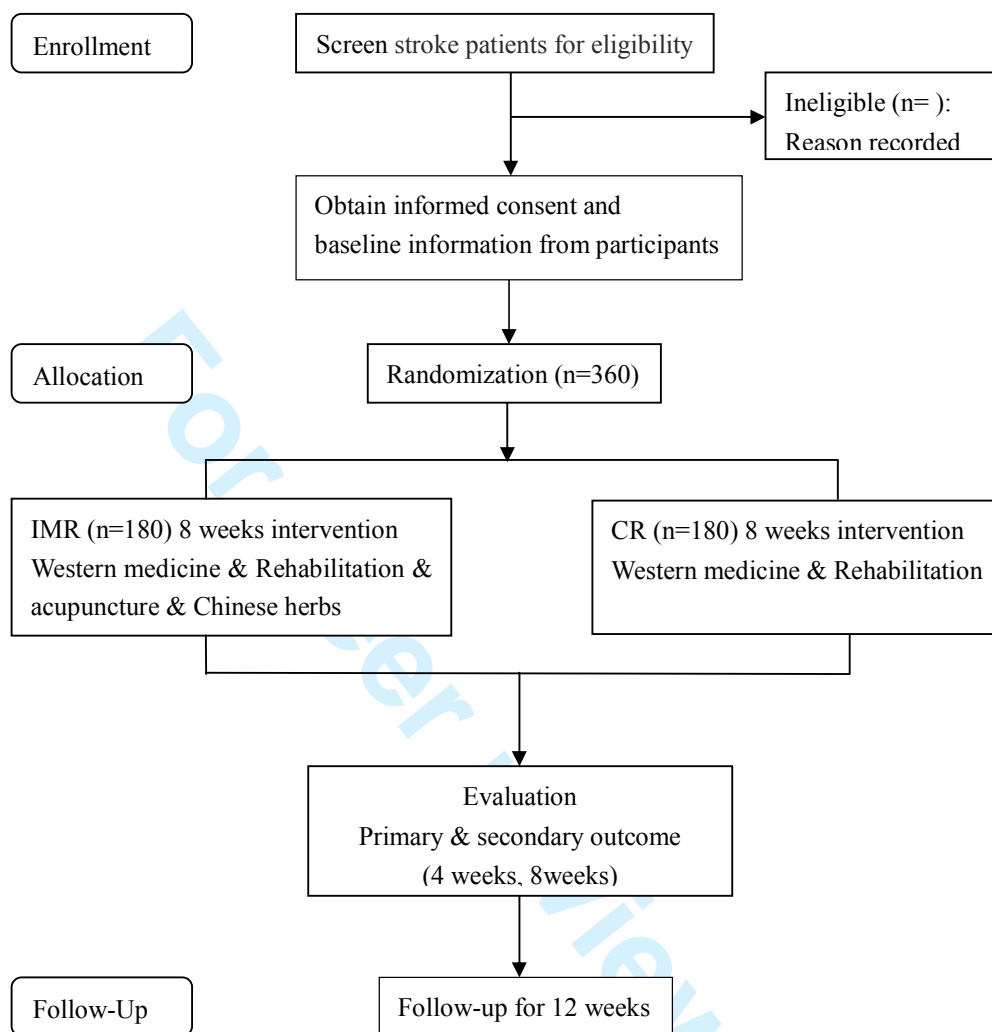


Figure 1.Route diagram of study design.

Participant recruitment

After getting the approval of Institutional Review Board, we recruited participants by advertising in local newspapers, health-related TV programs, Internet and posters in hospitals and communities. The recruiting time was from March 1, 2012 to December 31, 2014. The patients intending to join the study can consult with study coordinators regarding any questions they may have. Once the patients qualified and agreed to participate in the study, informed consent was obtained prior to running the series of baseline measurement assessments.

Inclusion criteria

To be eligible, participants must meet the following conditions: (1) Patients 35-80

1
2
3 years old, with a recent (30~40 days) ischemic stroke; (2) Patients with a NIHSS
4 score between 4 and 24; (3) The stroke should be the first incidence or patients can
5 have a history of stroke, but without disability (modified Rankin Scale, mRS score
6 ≤ 1).
7
8
9

10 11 **Exclusion criteria**

12 Participants who conform to any conditions below will be excluded: (1) Patients
13 received thrombolytic therapy or participated in other clinical trials in last three
14 months; (2) Patients who suffered from serious heart, liver, kidney related diseases,
15 blood coagulation dysfunction, or severe mental disorders; (3) Patients who can not
16 accept acupuncture, and(or) Chinese medicine treatment; (4) Women who are
17 pregnant or breast-feeding; (5) patients with congenital disabilities.
18
19
20
21
22
23

24 **Ethical considerations**

25 Each of the ethics committees of the Third Affiliated Hospital of Zhejiang Traditional
26 Chinese Medical University, Hangzhou Hospital of Traditional Chinese Medicine and
27 Jiaying Hospital of Traditional Chinese Medicine, all approved the study. The
28 purpose, nature, and potential risks of the experiments were fully explained to the
29 patients and their families. All patients gave their written and oral informed consent
30 before participating in the study.
31
32
33
34
35
36

37 **Randomization and blinding**

38 Randomization was done by Excel computer software in the study. The generated list
39 of random numbers was printed, cut into small pieces, separated and placed into
40 sequentially numbered, opaque, sealed envelopes. The envelopes were saved by the
41 special screeners. When the participant is included, the screeners opened the envelope
42 to get the group information. Then the subject was informed whether they would be in
43 the treatment group or control group, with or without acupuncture & Chinese herbs.
44 All of the rehabilitation therapists, outcome assessors, and data analysts are blinded to
45 group assignments. However, it is impossible to make acupuncturists blinded, because
46 they are trained to perform the treatment for participants of IMR group.
47
48
49
50
51
52
53
54
55

56 **Interventions and comparison**

1
2
3 The study is a randomized clinical trial carried out in three centers. Participants will
4 be randomized to either the IMR group or CR group. Both groups will receive
5 conventional stroke rehabilitation care, which includes normal limb posture,
6 physiotherapy (PT) and occupational therapy (OT), and/or cognitive training for
7 cognitive impairment, and/or psychological counseling for emotional disorder. The
8 rehabilitation team develops the rehabilitation program according to the investigator's
9 brochure. Rehabilitation includes physiotherapy and occupational therapy for two
10 hours per day, six days per week for each participant. The IMR group will receive 30
11 additional minutes of acupuncture therapy every day, six days per week and take
12 Chinese herbal decoction (twice a day) for eight weeks during the inpatient stay.

22 **Acupuncture treatment**

23
24 The acupuncture program, developed by experts of our project group after many
25 discussions, was performed by certified acupuncturists with more than five years of
26 clinical experience. To ensure the same condition, all of the treatment protocols and
27 processes are detailed below:
28
29

30
31 Scalp acupuncture: Select filiform needle (size 0.25 mm × 40 mm, Huatuo brand,
32 manufactured by Suzhou Medical Appliance in Suzhou, Jiangsu Province China),
33 swiftly insert the needle subcutaneously in 30° to the scalp on the top midline, the
34 motor area and the sensory area of the affected side.
35
36

37
38 Body acupuncture (the affected side): LI15 (JianYu), LI11 (QuChi), LI10
39 (ShouSanLi), SJ5 (WaiGuan), LI4 (HeGu) for upper limbs; ST32 (BiGuan), ST36
40 (ZuSanLi), GB34 (YangLingQuan), GB39 (XuanZhong), BL60 (KunLun) for lower
41 limbs. Acupoints of the above are referred to the People's Republic of China, State
42 Standard Name and Location of Acupoints (GB 12346-2006).
43
44

45
46 Modification according to dysfunction after stroke: For cognitive impairment
47 patients, add GV20 (BaiHui), GV24 (ShenTing), GB13 (BenShen), EX-HN1
48 (SiShenCong), Temple-Three-Needles (which is located in temple area, on the
49 opposite side of hemiplegia, the first needle is located in 2 cun straight above ear apex,
50 then the second and third needles are separately at the lateral 1 cun of the first needle).
51 For emotional disorder patients, add LR3 (TaiChong), PC6 (NeiGuan), GV20
52
53
54
55
56
57
58
59
60

(BaiHui), GV29 (YinTang), GV24 (ShenTing).

Modification according to syndrome differentiation: For disturbance of wind-fire type, add LR2 (XingJian), LR3 (TaiChong), LR14 (QiMen); For phlegm-stasis blocking collaterals, add SP10 (XueHai), ST40 (FengLong); For yin deficiency and wind act, add SP6 (SanYinJiao), KI3 (TaiXi), LR3 (TaiChong); For qi deficiency and blood stasis type, add CV6 (QiHai), CV4 (GuanYuan), BL17 (GeShu).

Electro-acupuncture will be used when the patients De Qi (the sensation of aching, numbness, tingling or warmth). Then, LI15 (JianYu) and LI11 (QuChi), ST36 (ZuSanLi) and GB39 (XuanZhong) will be connected to GB6805-2 Electro-Acu Stimulators (Huayi Medical Supply & Equipment Co., Ltd, Shanghai, China). The parameter is 2Hz intermittent wave at the intensity within patients' tolerance.

Syndrome differentiation and Chinese herbal medicine

The prescription of Chinese herbs is based on syndrome differentiation. We formulated the treatment protocol through textbooks and ancient literatures, as well as experts' experiences, and the final version of the protocol was used for stroke patients of three centers before the trial carried out. There are four types according to syndrome differentiation: (1)For the syndrome of disturbance of wind-fire, Prescription: Tian Ma Gou Teng decoction modified (Tian Ma 9g, Gou Teng 15g, Shi Jue Ming 15g, Shan Zhi Zi 9g, Huang Qin 9g, Chuan Niu Xi 15g, Du Zhong 12g, Yi Mu Cao 15g, Sang Ji Sheng 15g, Ye Jiao Teng 9g, Fu Sheng 9g, raw Long Gu 30g, raw Mu Li 30g); (2)For the syndrome of phlegm-stasis blocking collaterals, Prescription: Ban Xia Bai Zhu Tian Ma decoction and Tao Hong Si Wu decoction modified (Ban Xia 9g, Bai Zhu 9g, Tian Ma 9g, Fu Lin 9g, Ju Hong 6g, Sheng Di 15g, Dang Gui 15g, Chuan Xiong 9g, Tao Ren 9g, Hong Hua 6g) (3)For the syndrome of yin deficiency and wind act, Prescription: Zhen Gan Xi Feng decoction modified (raw Long Gu 15g, raw Mu Li 15g, Dai Zhe Shi 30g, Gui Ban 15g, Bai Shao 15g, Xuan Shen 15g, Tian Dong 15g, Chuan Lian Zi 6g, Yin Chen 6g, Chuan Xiong 15g, raw Mai Ya 6g, fried Gan Cao 6g) (4)For the syndrome of qi deficiency and blood stasis, Prescription: Bu Yang Huan Wu decoction modified (raw Huang Qi 30g, Dang Gui 15g, Tao Ren 6g, Hong Hua 6g, Di Long 12g, Chi Shao 15g).

Conventional Rehabilitation Group

Patients in CR group do not receive acupuncture and Chinese herbs. This group only receives basic Western medical and rehabilitation treatment, in the same frequency, with the same course of treatment as the IMR group.

Outcome assessment

The assessment data will be collected at baseline, 4 and 8 weeks post-randomization, and then 12 weeks after completing the treatment.

Baseline assessment

Demographic data includes gender, age, nationality, education level, occupation, and marital status. Information on stroke risk factors regarding smoking, drinking, height, weight, blood pressure, family history of stroke, blood lipids, and blood sugar is gathered through review of the medical records. Several classifications of disease data regarding: rehabilitation evaluation scales on neurological deficit, sensory motor, cognitive, and emotional disorders will be also analyzed before randomization.

Primary outcome measurement

The primary outcome measurement is the Modified Barthel Index (MBI), which was developed in 1955 as a simple index of independence useful in scoring disability⁸. The MBI scale is a reliable measure of functional independence. It is sensitive and valid to evaluate dependence in the activities of daily living (ADL). It includes ten variables (defecating, urinating, feeding, bathing, grooming, dressing, toileting, transfer, walking, and stairs) describing ADL and mobility. A higher number is associated with a greater likelihood of being able to live at home with a degree of independence. This index is used as a standardized assessment on rehabilitation wards and also as standardized follow-up assessment to determine whether gains achieved by patients with stroke while hospitalized are maintained after discharge⁹⁻¹¹.

Secondary outcome measures

The National Institutes of Health Stroke Scale (NIHSS) for neurologic deficits

The National Institutes of Health Stroke Scale (NIHSS) is a graded neurological examination that assesses consciousness, best gaze, visual field, facial palsy, motor arm, motor leg, limb ataxia, sensory, best language, dysphagia, and neglect. The scale

1
2
3 was developed for use in acute-stroke trials, and has since been widely used as
4 a standard part of the assessment in clinical trials. Its scores range is from 0 to 42, with
5 scores above 25 indicating very severe neurological impairment, scores of 5 to 24
6 suggesting moderately severe to severe impairment, and scores below 5 indicate mild
7 impairment¹²⁻¹³.

12 **The Fugl-Meyer Assessment (FMA) scale for motor dysfunction**

14 The FMA was developed as the first quantitative evaluative instrument for measuring
15 sensorimotor stroke recovery, which includes items dealing with the shoulder, elbow,
16 forearm, wrist, and hand in the upper extremity (UE, 66 points) and the hip, knee, and
17 ankle in the lower extremity (LE, 34 points)¹⁴. The motor domain has well-established
18 reliability and validity as an indicator of motor impairment severity across different
19 stroke recovery time points¹⁵.

26 **The Mini-Mental State Examination (MMSE) and Montreal Cognitive 27 Assessment (MoCA) for cognitive impairment**

29 Cognitive function is assessed by MMSE and MoCA scale. MMSE is a brief
30 wide-range screening test with 30 aggregate scores, which is more suitable for
31 uneducated or old populations. It assesses memory, orientation, calculation, attention,
32 expressing, and reading. In fact, MMSE is widely used because of its high specificity,
33 but it can't subtly detect mild cognitive impairment (MCI) patients, whose scores are
34 in the normal range¹⁶. In contrast, MoCA is more sensitive. It is also a test with 30
35 points, of which items including visual-spatial abilities, executive functions, attention,
36 concentration, memory, language, orientation. The MoCA detects MCI patients with
37 90% sensitivity and 87% specificity¹⁷.

46 **The Self-Rating Depression Scale (SDS) and Hamilton's Depression Scale 47 (HAMD) for emotional disorder**

49 SDS is a self-report instrument covering 20 items, either positive or negative, with a
50 four-point scale ranging from 1 to 4. The standardized score is the total score times
51 1.25, which results in 25 to 100¹⁸. Furthermore, in antidepressant clinical trials, the
52 Hamilton Depression Rating Scale has been the "gold standard" for use¹⁹. The
53 HAMD Scale we selected includes 24 items, consisting of sense of guilt, sleeping
54
55
56
57
58
59
60

1
2
3 problems, suicide, interest, anxiety, loss of weight, self-abasement, hopelessness, and
4 so on, 14 items with a score of 0-4 and 10 items with score of 0-2. The range of scores
5 for the whole test is 0-76. Higher scores indicate a higher level of mental disorder,
6 respectively²⁰.

11 **The incidence of adverse events**

12 Participants are to be questioned and report all adverse events (AEs) at each visit
13 point, and all AEs reports will be recorded and assessed by the investigators. If serious
14 adverse events happen, the researchers should report to the principal investigator and
15 ethics committee immediately, who will make a decision on whether the participant
16 needs to withdraw from the study. *If the participant suffered serious adverse events,
17 unbinding is permissible, and procedure is followed for revealing a participant's
18 allocated intervention during the trial. Compensation will be provided to those who
19 suffer harm from trial participation.*

20
21 In order to assess the safety of herbal medicine, we will perform the following
22 tests on participants of IMR group at the baseline (week 0) and after treatment (week
23 12): blood routine test, urine routine test, feces routine test, kidney function test, liver
24 function test. In addition, investigators will ask every subject at each visit whether
25 they have experienced allergies or gastrointestinal discomfort during the study period.

26
27 The adverse events of acupuncture may include local bleeding, hematoma, pallor,
28 sweating or dizziness, fainting during the acupuncture treatment, unbearable pricking,
29 retained needle after treatment. The investigator should record the date of occurrence,
30 time, degree, measurement related to the treatment, and consequence.

37 **Quality control and data management**

38
39 This is a 20-week clinical trial, in which participants need to take herbal medicine and
40 acupuncture for 8 weeks, and accept a 12-week follow-up, attend four assessment
41 visits (rehabilitation evaluation), obtain one set of laboratory tests (safety
42 assessments), Before the study, the trial protocol has been reviewed and revised by
43 experts on acupuncture, neurology, rehabilitation, statistics, and methodology several
44 times. All the members belonging to the trial are asked to take part in a series of
45 training to ensure that the personnel involved fully understand the research protocol

1
2
3 and standard operating procedures for the study. During the study, the Clinical
4 Research Institute of Zhejiang Provincial is responsible for **generating the allocation**
5 **sequence**, quality control, and censors have regular visits (once a month) to monitor
6 protocol violations, the recruitment rate, AEs and participant compliance. **This clinical**
7 **trial is independent from sponsors and competing interests.** The clinical coordinators
8 of three centers are specifically designated to enroll participants, and assign
9 participants to interventions, but not to participate in treatment and assessment for
10 subjects. Outcome assessors and data analysts will be blinded after assignment to
11 interventions, without access to patients' group information.

12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
The measurements are mainly rehabilitation evaluations. All of the data will first
be recorded on the paper version of the case report form (CRF) by assessors, then
double entered into EDC system electronically. A specified statistics centre of the
Clinical Research Institute of Zhejiang Province will responsible for data management.
All data will be double entered to ensure accuracy. The source of any inconsistencies
will be explored and resolved.

Sample size calculation

The primary efficacy parameter is the change in MBI scores from baseline to the end
of treatment after eight weeks. Sample size calculations are based on our preliminary
test and previous study²¹⁻²², The expected difference between CR group and IMR
group is 10 value, it is to say the score of MBI of IMR group was 10 value higher than
that of CR group, and the standard deviation is about 31, A two-sided 5% significance
level and 80% power were considered, and the following equation was used:

$$n = \frac{2 \left(\frac{z_{\alpha}}{2} + z_{\beta} \right)^2 \sigma^2}{\Delta^2}$$

Approximately 150 participants in each group were calculated to be required.
Estimating a 20% dropout rate, each group will require 180 initial participants.

Statistical analysis

Efficacy and safety analyses will be conducted according to the intention-to-treat (ITT)
principle by a statistician blinded to group allocation. Missing values will be imputed

1
2
3 by the last-observation-carried-forward method. All statistical analyses will be
4 performed using Statistical Product and Service Solutions (SPSS) statistical package
5 program (ver. 17.0, SPSS Inc., Chicago, IL, USA). The primary outcomes (MBI) and
6 FMA will undergo ITT analysis including all the patients who are randomized. The
7 analysis of cognitive impairment, emotional disorder will be made among the defined
8 population of corresponding dysfunction. Continuous variables will be expressed as
9 means with standard deviations. For normally distributed variables, two independent
10 samples will be compared by t-test. On the other hand, for abnormally distributed
11 variables, Non-parametric tests will be used, and the data will be expressed as
12 medians with ranges. A P-value of less than 0.05 is considered as statistical
13 significance. Safety analysis is based on the frequency of adverse events relating to
14 the treatment.

25 DISCUSSION

26
27 China's extensive clinical experience in the use of traditional Chinese medicines in
28 stroke therapy indicates that TCM preparations are effective. More than 100
29 traditional medicines are currently in use for stroke therapy in China²³. However,
30 insufficient good-quality evidence on the effects of TCM in ischemic stroke exists on
31 the primary outcome²⁴. One possibility for lack of evidence in the literature could
32 result from the significant clinical and methodological heterogeneity, preventing
33 effective meta-analysis techniques. No meta-analysis have been performed and thus
34 no cumulative results obtained by pooling RCT data exist²⁵. Further randomized
35 controlled trials are justified.

36
37
38
39
40
41
42 Acupuncture is recommended for stroke according to the World Health
43 Organization²⁶. Literature reviews have demonstrated the safety of acupuncture,
44 legitimizing its ethical use for patients, without causing harm⁷. Despite its safety, the
45 limited availability of rigorous RCTs and the lack of research available on
46 complementary and alternative medicine treatments like acupuncture, create a
47 controversial opinion on its benefit for specific disease outcomes^{7,27-28}. This lack of
48 evidence necessitates additional RCT study on the clinical efficacy of integrative
49 medicine on stroke outcomes.

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

Complementary or termed alternative medicine such as acupuncture and Chinese medicine, or integrative medicine has become increasingly prevalent and popular, not only in China, but also worldwide²⁹⁻³⁰. Integrated traditional Chinese and Western medicine for stroke rehabilitation is widely used in China, making it an ideal setting to study stroke treatment protocols. The integrated approach is forming some of China characteristics of stroke treatment modalities, which can be observed as a model for the rest of the world³¹. Many patients in China, with stroke, receive basic Western medicine and rehabilitation as well as acupuncture and Chinese medicine during hospital stays. So we are conducting this clinical trial, which is close to the actual treatment strategy in China, to objectively evaluate the clinical efficacy. Syndrome differentiation and treatment is the essence of Chinese medicine, so in our study, Chinese herbal prescriptions for stroke patients are clarified. Four types of herbal medicine are most common in clinic according to syndrome differentiation. The acupuncture program traditionally includes scalp acupuncture and body acupuncture, and in addition some acupoints are selected according to the patient's dysfunction and also syndrome differentiation. Under strict quality control, this study could potentially confirm whether or not integrative medicine (IM) is an effective adjunct to the standard rehabilitation therapy for ischemic stroke. Our study may also assess the efficacy of IM in promoting the recovery of motor dysfunction, cognitive impairment and emotional disorder.

CONCLUSION

This trial has been designed to provide robust data on the efficacy of integrative medicine for patients with ischemic stroke. It is also expected to clarify whether or not integrative medicine is effective for motor, cognitive, or emotional disorder after stroke.

Trial status

The trial is currently enrolling participants; recruitment started in March 1, 2012 and will be completed in December 31, 2014.

List of abbreviations used

FMA, Fugl-Meyer Assessment; MCI, Mild Cognitive Impairment; MMSE,

1
2
3 Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NIHSS,
4 National Institutes of Health Stroke Scale; VFSS, Video-fluoroscopic Swallowing
5 Study; SPSS, Statistical Product and Service Solutions; mRS, modified Rankin Scale;
6
7
8
9 IMR, integrative medicine rehabilitation; CR, conventional rehabilitation; MBI,
10 Modified Barthel Index; ADL, activities of daily living; HAMD, Hamilton's
11 Depression Scale; SDS, Self-Rating Depression Scale; AEs, adverse events; TCM,
12 traditional Chinese medicine; PT, physiotherapy; OT, occupational therapy; IM,
13 integrative medicine.
14
15
16
17

18 **Competing interests**

19
20 The authors declare that they have no competing interests.
21

22 **Authors' contributions**

23
24 JQF, LFC, LNC, CW, CLK and CHJ and participated in the conception and design of
25 the trial, planning the analysis of the data and drafting the manuscript. RJM, SYX, LHS,
26 and YHB participated in data collection and are in charge of recruitment and treatment
27 of patients in each center. All the authors discussed, revised and approved the final
28 manuscript.
29
30
31
32

33 **Authors' information**

34
35 ¹ Department of Acupuncture, The Third Affiliated Hospital of Zhejiang Traditional
36 Chinese Medical University, No. 219 Moganshan Road, XiHu District, Hangzhou,
37 Zhejiang Province 310005, China
38
39

40
41 ² The Third Clinical Medical College of Zhejiang Traditional Chinese Medical
42 University, No. 548 Binwen Road, Binjiang District, Hangzhou, Zhejiang Province
43 310053, China
44
45

46
47 ³ Innovations to Wellness. Affiliated with Five Branches University. 3031 Tisch Way,
48 5th floor Administration. San Jose, CA, 95128.
49

50
51 ⁴ Department of Rehabilitation, The Third Affiliated Hospital of Zhejiang Traditional
52 Chinese Medical University, No. 219 Moganshan Road, XiHu District, Hangzhou,
53 Zhejiang Province 310005, China
54
55
56
57
58
59
60

⁵ Department of Acupuncture & Encephalopathy, Jiaying Hospital of Traditional Chinese Medicine. No. 1501 Zhongshan East Road, Jiaying, Zhejiang Province 310012, China

⁶ Department of Acupuncture & Rehabilitation, Hangzhou Hospital of Traditional Chinese Medicine. No. 453 Tiyuchang Road, XiHu District, Hangzhou, Zhejiang Province 310007, China

⁷ The Clinical Research Institute of Zhejiang Provincial Hospital of Traditional Chinese Medicine, No. 54 Youdian Road, Hangzhou, Zhejiang Province 310006, China

Acknowledgements and Funding

This study is funded by a project grant from the Provincial Administration of Traditional Chinese Medicine of Zhejiang (2011ZGG003), and the funder will not have a role in the conduction or interpretation of this trial, or in any decision to publish the results. The team would like to thank three postgraduate students who contributed their time to the preliminary experiments (Pei Luo, Wei Dong, and Lu Zhang). We also appreciate the help and effort from the people participating in this trial.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/3.0/>

References

1. Bonita R, Mendis S, Truelsen T, *et al*. The global stroke initiative. *The Lancet Neurology* 2004; 3(7):391–393.
2. Wang L, Kong L, Wu F, *et al*. Preventing chronic diseases in China. *The Lancet* 2005; 366(9499):1821–1824.

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
3. Liu M, Wu B, Wang WZ, *et al.* Stroke in China: epidemiology, prevention, and management strategies. *The Lancet Neurology* 2007; 6(5):456–464.
 4. Liu L, Wang D, Wong KS, *et al.* Stroke and stroke care in China: huge burden, significant workload, and a national priority. *Stroke* 2011; 42:3651–3654.
 5. Zhao D, Liu J, Wang W, *et al.* Epidemiological Transition of Stroke in China Twenty-One-Year Observational Study From the Sino-MONICA-Beijing Project. *Stroke* 2008; 39:1668–1674.
 6. Wang J, Xiong X. Current situation and perspectives of clinical study in integrative medicine in China. *Evidence-Based Complementary and Alternative Medicine* 2012; 2012.
 7. Wu HM, Tang JL, Lin XP, *et al.* Acupuncture for stroke rehabilitation. *Stroke* 2008; 39(2):517–518.
 8. Mahoney FI. Functional evaluation: the Barthel index. *Maryland State Medical Journal* 1965; 14:61–65.
 9. Collin C, Wade DT, Davies S, *et al.* The Barthel ADL Index: a reliability study. *Disability & Rehabilitation* 1988; 10(2):61–63.
 10. Granger CV, Dewis LS, Peters NC, *et al.* Stroke rehabilitation: analysis of repeated Barthel index measures. *Archives of physical medicine and rehabilitation* 1979; 60(1):14–17.
 11. Loewen SC, Anderson BA. Reliability of the modified motor assessment scale and the Barthel index. *Physical Therapy* 1988; 68(7):1077–1081.
 12. Adams HP Jr, Davis PH, Leira EC, *et al.* Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* 1999; 53:126–131.
 13. Goldstein LB, Samsa GP. Reliability of the National Institutes of Health Stroke Scale extension to non-neurologists in the context of a clinical trial. *Stroke* 1997; 28(2):307–310.
 14. Sanford J, Moreland J, Swanson LR, *et al.* Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. *Physical therapy* 1993; 73(7):447–454.

15. Sullivan KJ, Tilson JK, Cen SY, *et al.* Fugl-Meyer assessment of sensorimotor function after stroke: Standardized training procedure for clinical practice and clinical trials. *Stroke* 2011; 42:427–432.
16. Wind AW, Schellevis FG, Van Staveren G, *et al.* Limitations of the Mini-Mental State Examination in diagnosing dementia in general practice[J]. *International journal of geriatric psychiatry* 1997;12(1): 101-108.
17. Nasreddine ZS, Phillips NA, Bédirian V, *et al.* The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* 2005; 53(4):695–699.
18. Bose M, Shah P. Analyzing Post Stroke Depression (PSD) Levels in Stroke Patients Using Zung Self-Rating Depression Scale. *Indian Journal of Physiotherapy and Occupational Therapy-An International Journal* 2012; 6(4):187–190.
19. McIntyre RS, Konarski JZ, Mancini DA, *et al.* Measuring the severity of depression and remission in primary care: validation of the HAMD–7 scale. *Canadian Medical Association Journal* 2005;173(11):1327–1334.
20. Williams JBW, Kobak KA, Bech P, *et al.* The GRID-HAMD: standardization of the Hamilton depression rating scale. *International clinical psychopharmacology* 2008; 23(3):120–129.
21. Gosman-Hedström G, Claesson L, Klingenstierna U, *et al.* Effects of acupuncture treatment on daily life activities and quality of life a controlled, prospective, and randomized study of acute stroke patients. *Stroke* 1998; 29(10):2100–2108.
22. Park J, White AR, James MA, *et al.* Acupuncture for subacute stroke rehabilitation: a sham-controlled, subject-and assessor-blind, randomized trial. *Archives of internal medicine* 2005; 165(17):2026–2031.
23. Gong X, Sucher NJ. Stroke therapy in traditional Chinese medicine (TCM): prospects for drug discovery and development. *Trends in pharmacological sciences* 1999; 20(5):191–196.
24. Wu B, Liu M, Liu H, *et al.* Meta-analysis of traditional Chinese patent medicine for ischemic stroke. *Stroke* 2007; 38(6):1973–1979.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
25. Junhua Z, Menniti-Ippolito F, Xiumei G, *et al.* Complex traditional Chinese medicine for post stroke motor dysfunction a systematic review. *Stroke* 2009; 40(8):2797–2804.
 26. World Health Organization S: Acupuncture: Review and analysis of reports on controlled clinical trials. Geneva, Switzerland: *World Health Organization* 2003.
 27. Zhang SH, Liu M, Asplund K, *et al.* Acupuncture for acute stroke. *Stroke* 2005; 36:2327–2328.
 28. Sze FK, Wong E, Or KKH, *et al.* Does acupuncture improve motor recovery after stroke? A meta-analysis of randomized controlled trials. *Stroke* 2002; 33(11):2604–2619.
 29. Fontanarosa PB, Lundberg GD. Complementary, alternative, unconventional, and integrative medicine: call for papers for the annual coordinated theme issues of the AMA journals. *JAMA* 1997; 278(23):2111–2112.
 30. Maizes V, Rakel D, Niemiec C. Integrative medicine and patient-centered care. *Explore: The Journal of Science and Healing* 2009; 5(5):277–289.
 31. Wang J, Xiong X. Current situation and perspectives of clinical study in integrative medicine in China. *Evidence-Based Complementary and Alternative Medicine* 2012; 2012.



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

| Section/item | Item No | Description |
|-----------------------------------|---------|--|
| Administrative information | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym [page 1] |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry [page 3] |
| | 2b | All items from the World Health Organization Trial Registration Data Set [page 3. See detail in URL http://www.chictr.org/en/proj/show.aspx?proj=2561] |
| Protocol version | 3 | Date and version identifier [Date: Jun 15,2012 ;Version identifier:4.0] |
| Funding | 4 | Sources and types of financial, material, and other support [page 15] |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors [pages 14-15] |
| | 5b | Name and contact information for the trial sponsor [page 15] |
| | 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 [page 15] |
| | 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) [page 11] |
| 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 [pages 2-4] |
| | 6b | Explanation for choice of comparators [pages 2-4] |

| | | | |
|---|--------------|---|--|
| 1 | Objectives | 7 | Specific objectives or hypotheses [pages 2-4] |
| 2 | | | |
| 3 | Trial design | 8 | Description of trial design including type of trial (eg, parallel group, |
| 4 | | | rossover, factorial, single group), allocation ratio, and framework (eg, |
| 5 | | | superiority, equivalence, noninferiority, exploratory) [pages 4-5] |
| 6 | | | |
| 7 | | | |
| 8 | | | |
| 9 | | | |

Methods: Participants, interventions, and outcomes

| | | | |
|----|----------------------|-----|--|
| 10 | | | |
| 11 | Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) |
| 12 | | | and list of countries where data will be collected. Reference to where |
| 13 | | | list of study sites can be obtained [pages 6] |
| 14 | | | |
| 15 | | | |
| 16 | Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility |
| 17 | | | criteria for study centres and individuals who will perform the |
| 18 | | | interventions (eg, surgeons, psychotherapists) [pages 6] |
| 19 | | | |
| 20 | Interventions | 11a | Interventions for each group with sufficient detail to allow replication, |
| 21 | | | including how and when they will be administered [pages 7-9] |
| 22 | | | |
| 23 | | 11b | Criteria for discontinuing or modifying allocated interventions for a |
| 24 | | | given trial participant (eg, drug dose change in response to harms, |
| 25 | | | participant request, or improving/worsening disease) [page 11] |
| 26 | | | |
| 27 | | 11c | Strategies to improve adherence to intervention protocols, and any |
| 28 | | | procedures for monitoring adherence (eg, drug tablet return, |
| 29 | | | laboratory tests) [pages 11-12] |
| 30 | | | |
| 31 | | 11d | Relevant concomitant care and interventions that are permitted or |
| 32 | | | prohibited during the trial [pages 11-12] |
| 33 | | | |
| 34 | | | |
| 35 | Outcomes | 12 | Primary, secondary, and other outcomes, including the specific |
| 36 | | | measurement variable (eg, systolic blood pressure), analysis metric |
| 37 | | | (eg, change from baseline, final value, time to event), method of |
| 38 | | | aggregation (eg, median, proportion), and time point for each |
| 39 | | | outcome. Explanation of the clinical relevance of chosen efficacy and |
| 40 | | | harm outcomes is strongly recommended [pages 9-11] |
| 41 | | | |
| 42 | | | |
| 43 | Participant | 13 | Time schedule of enrolment, interventions (including any run-ins and |
| 44 | timeline | | washouts), assessments, and visits for participants. A schematic |
| 45 | | | diagram is highly recommended (see Figure) [page 5-11, See detail in |
| 46 | | | Figure. Content for the schedule of enrolment, interventions, and |
| 47 | | | assessments] |
| 48 | | | |
| 49 | | | |
| 50 | Sample size | 14 | Estimated number of participants needed to achieve study objectives |
| 51 | | | and how it was determined, including clinical and statistical |
| 52 | | | assumptions supporting any sample size calculations [page 12] |
| 53 | | | |
| 54 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach |
| 55 | | | target sample size [page 5] |
| 56 | | | |
| 57 | | | |
| 58 | | | |
| 59 | | | |
| 60 | | | |

Methods: Assignment of interventions (for controlled trials)

Allocation:

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
- | | | |
|----------------------------------|-----|---|
| 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 [page 6] |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned [page 6] |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions [page 12] |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how [page 12] |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial [page 11] |

Methods: Data collection, management, and analysis

- 29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- | | | |
|-------------------------|-----|--|
| 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 [page 12] |
| | 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 [pages 12-13] |
| 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 [page 12] |
| 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 [pages 12-13] |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) [pages 12-13] |

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

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) [\[pages 12-13\]](#)

Methods: Monitoring

Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed [\[page 12\]](#)

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 [\[page 11\]](#)

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 [\[page 11\]](#)

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor [\[page 11\]](#)

Ethics and dissemination

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval [\[pages 2,6\]](#)

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) [\[page 11\]](#)

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) [\[page 6\]](#)

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable [\[page 6\]](#)

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 [\[page 6\]](#)

Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site [\[page 14\]](#)

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 [\[page 16\]](#)

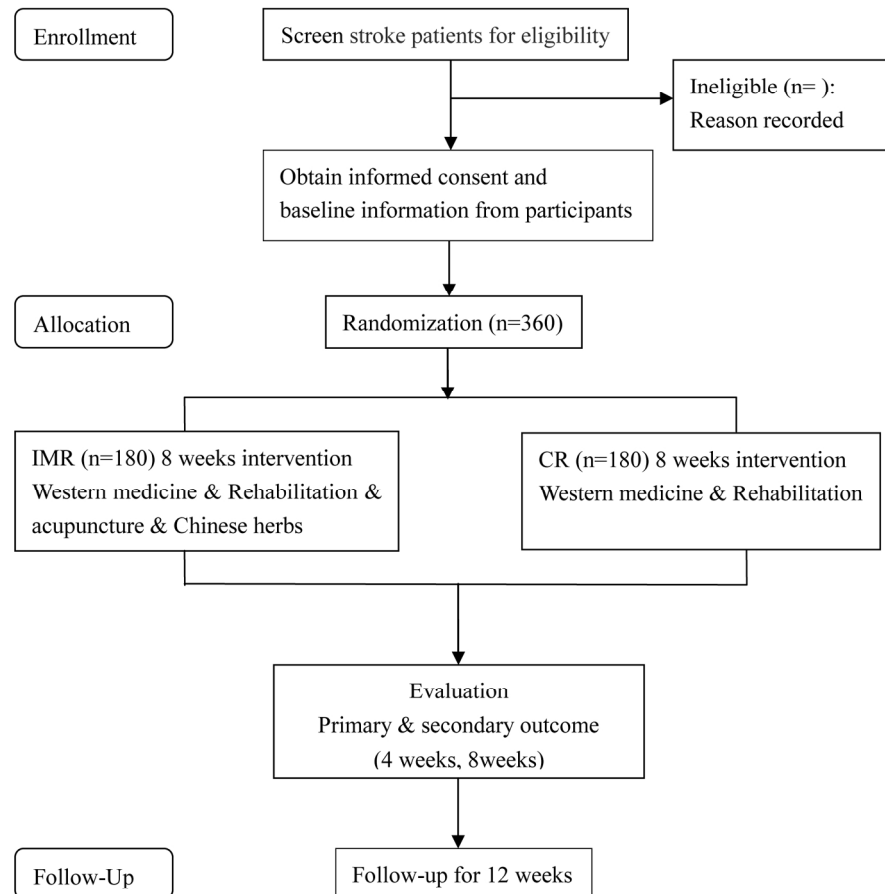
| | | | |
|----|-------------------|-----|--|
| 1 | | | |
| 2 | Ancillary and | 30 | Provisions, if any, for ancillary and post-trial care, and for |
| 3 | post-trial care | | compensation to those who suffer harm from trial participation [page |
| 4 | | | 11] |
| 5 | | | |
| 6 | Dissemination | 31a | Plans for investigators and sponsor to communicate trial results to |
| 7 | policy | | participants, healthcare professionals, the public, and other relevant |
| 8 | | | groups (eg, via publication, reporting in results databases, or other |
| 9 | | | data sharing arrangements), including any publication restrictions |
| 10 | | | [pages 2-3] |
| 11 | | | |
| 12 | | 31b | Authorship eligibility guidelines and any intended use of professional |
| 13 | | | writers [page 15] |
| 14 | | | |
| 15 | | 31c | Plans, if any, for granting public access to the full protocol, participant- |
| 16 | | | level dataset, and statistical code [page 16] |
| 17 | | | |
| 18 | | | |
| 19 | Appendices | | |
| 20 | | | |
| 21 | Informed consent | 32 | Model consent form and other related documentation given to |
| 22 | materials | | participants and authorised surrogates [pages 5-6] |
| 23 | | | |
| 24 | Biological | 33 | Plans for collection, laboratory evaluation, and storage of biological |
| 25 | specimens | | specimens for genetic or molecular analysis in the current trial and for |
| 26 | | | future use in ancillary studies, if applicable [page 11] |
| 27 | | | |

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

Figure. Content for the schedule of enrolment, interventions, and assessments

| | STUDY PERIOD | | | | |
|---|--------------|------------|-----------------|---------|-----------|
| | Enrolment | Allocation | Post-allocation | | Close-out |
| | TIMEPOINT** | 0 | 4 weeks | 8 weeks | 12weeks |
| ENROLMENT: | | | | | |
| Eligibility screen | X | | | | |
| Informed consent | X | | | | |
| Baseline assessment | X | | | | |
| Allocation | | X | | | |
| INTERVENTIONS: | | | | | |
| IMR group | | | ↔ | | |
| CR group | | | ↔ | | |
| ASSESSMENTS: | | | | | |
| Demographic data | X | X | | | |
| MBI | | X | X | X | X |
| NIHSS | | X | X | X | X |
| FMA | | X | X | X | X |
| MMSE & MoCA | | X | X | X | X |
| SDS & HAMD | | X | X | X | X |
| AEs | | | X | X | |
| blood routine test, urine routine test, feces routine test, kidney function test, liver function test | | X | | X | |

Figure 1.Route diagram of study design.



161x176mm (300 x 300 DPI)

