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# BMJ Open

## The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for subacute stroke patients: a randomized controlled trial protocol

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SCHOLARONE™  
Manuscripts

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4 1 **The effectiveness of cerebellar vermis intermittent theta burst**  
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7 2 **stimulation in improving trunk control and balance function for**  
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10 3 **subacute stroke patients: a randomized controlled trial protocol**  
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3 16  
4 17 **Abstract**

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7 18 **Introduction** Balance impairments frequently occur in patients with stroke. Achieving  
8  
9 19 effective core trunk stability is the key to improving balance ability. However, there still lacks  
10  
11 20 of advanced well-defined rehabilitation protocols for balance improvement in stroke patients.  
12  
13 21 Intermittent theta-burst stimulation (iTBS) is a non-invasive brain activity modulation  
14  
15 22 strategy, which can produce long-term potentiation. Cerebellar vermis is a cardinal structure  
16  
17 23 involved in balance and motor control. However, no study has demonstrated the therapeutic  
18  
19 24 effect and potential mechanism of cerebellar vermis iTBS on balance in individuals with  
20  
21 25 stroke.

22  
23  
24  
25 26 **Methods and Analysis** This study will be a prospective single-center double-blind  
26  
27 27 randomized controlled clinical trial with 3-week intervention and 3-week follow-up. Eligible  
28  
29 28 participants will be randomly allocated in a 1:1 ratio to experimental group or control group,  
30  
31 29 respectively. After routine conventional physical therapy, patients assigned to the  
32  
33 30 experimental group will receive cerebellar vermis iTBS whereas patients assigned to the  
34  
35 31 control group will receive sham stimulation. The overall intervention periods are five days a  
36  
37 32 week for three consecutive weeks. The outcomes will be measured at baseline (T0), 3 weeks  
38  
39 33 post-intervention (T1) and 3 weeks follow-up (T3). The primary outcomes are Berg balance  
40  
41 34 scale (BBS) and trunk impairment scale (TIS) scores. The secondary outcomes are balance  
42  
43 35 tests via the Balance Master system, muscle activation of trunk and lower limbs via the  
44  
45 36 surface electromyography (sEMG) recording, cerebral cortex oxygen concentrations via the  
46  
47 37 resting-state functional near-infrared spectroscopy (fNIRS), FMA-LE scores, and Barthel  
48  
49 38 index (BI) scores.

50  
51 39 **Ethics and Dissemination** This study was approved by the West China Hospital Clinical  
52  
53 40 Trials and Biomedical Ethics Committee of Sichuan University. The trial registration number

1  
2  
3 41 is ChiCTR2200061225. All participants will sign the informed consent voluntarily. The  
4  
5 42 results of this study will be published in peer-reviewed journals and disseminated at academic  
6  
7 43 conferences.  
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9

#### 10 44 **Strengths and limitations of this study**

- 11  
12 45 ➤ This prospective single-center double-blind randomized controlled clinical trial with 3-  
13  
14 46 week intervention and 3-week follow-up is firstly designed to confirm the effect and  
15  
16 47 potential mechanism of cerebellar vermis iTBS stimulation on balance in subacute stroke  
17  
18 48 patients.  
19  
20 49 ➤ Our study will comprehensively assess the trunk control and balance function by clinical  
21  
22 50 scales, balance tests via the Smart Equitest Balance Master System and sEMG  
23  
24 51 measurements. Additionally, we will also collect the concentration of HbO<sub>2</sub> in cerebral  
25  
26 52 cortex via the resting-state fNIRS. Integrated data results sufficiently verify the research  
27  
28 53 hypothesis.  
29  
30 54 ➤ Our study can provide valuable information to develop a novel treatment method for the  
31  
32 55 rehabilitation of balance dysfunction after stroke.  
33  
34 56 ➤ This study has sufficient research basis. Previously published articles by our research  
35  
36 57 group provided evidence that iTBS of the cerebellar hemisphere could promotes upper  
37  
38 58 limb spasticity, balance, and walking performance recovery in post-stroke patients. And,  
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40 59 preliminary pilot study conducted by us found that cerebellar vermis iTBS contributed to  
41  
42 60 increasing the excitability of the bilateral supplementary motor areas during balance tasks  
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44 61 in healthy adults.  
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#### 52 62 **Introduction**

53  
54 63 Stroke is the third most common cause of disability worldwide.<sup>1</sup> The number of incidents,  
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56 64 prevalent survivors, and disability-adjusted life-years lost of stroke is still increasing over the  
57  
58 65 past two decades<sup>2</sup>, which are considered to lead to heavy economic burdens on society.  
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3 66 Balance impairments frequently occur in patients with stroke, with the reported incidence  
4  
5 67 ranging from 61% to 83%<sup>3</sup>. The main manifestations are postural instability, weak trunk  
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7 68 control, and difficulty of weight shift,<sup>4</sup> which will ultimately result in falls, poor mobility,  
8  
9 69 decreased physical activity, and reduced quality of life in patients.<sup>5</sup> Therefore, improvement  
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11  
12 70 of the balance function is a cardinal requirement in patients with stroke.

13  
14 71 The trunk plays a fundamental role in trunk control, balance, and mobility during sitting and  
15  
16 72 transferring.<sup>6</sup> The synchronized activity of trunk muscles is necessary for maintaining  
17  
18 73 dynamic balance. In addition, proper trunk muscle control is essential in stabilizing distal  
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20 74 limbs.<sup>7</sup> Muscle weakness of lower limbs is associated with a decreased standing balance  
21  
22 75 control.<sup>8</sup> Impaired trunk control and core muscle weakness attenuate balance and physical  
23  
24 76 function in individuals after stroke.<sup>9</sup> Therefore, achieving effective core trunk stability is  
25  
26 77 crucial to improving balance ability after stroke.

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29  
30 78 The cerebellum, a central brain structure located in posterior cranial fossa, works in concert  
31  
32 79 with the cerebral cortex, brainstem, and spinal cord and is involved in motor control.<sup>10 11</sup> It  
33  
34 80 consists of two lateral hemispheres and a cerebellar vermis. Cerebellar vermis is a cardinal  
35  
36 81 structure involved in balance and motor processing,<sup>12 13</sup> which is responsible for regulating  
37  
38 82 the trunk, head, neck and proximal limb muscles to control posture and maintain balance.<sup>14</sup>  
39  
40 83 And balance dysfunction in cerebellar disorders is most likely caused by lesions of the medial  
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42 84 zone of the cerebellum.<sup>15</sup> At present, the main clinical interventions to improve the balance  
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44 85 function in stroke rehabilitation are muscle strength training or balance training. It has a great  
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46 86 potential to activate the cerebellar vermis in the central nervous system through the  
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48 87 neuromodulation with non-invasive brain stimulation to enhance the balance function in  
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50 88 stroke patients.

51  
52 89 Repetitive transcranial magnetic stimulation (rTMS) is a safe, reliable, and standardized non-  
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54 90 invasive brain activity modulation strategy to regulate cortical excitability and facilitate neural  
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3 91 plasticity.<sup>16</sup> Intermittent theta-burst stimulation (iTBS) is a novel form of rTMS, which can  
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5 92 produce long-term potentiation and is more rapid and efficacious than standard rTMS.<sup>17</sup> Our  
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7 93 group recently provided evidence that iTBS of the cerebellar hemisphere could promotes  
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9 94 upper limb spasticity, balance, and walking performance recovery in post-stroke patients.<sup>18-20</sup>  
10  
11 95 However, no study has demonstrated the therapeutic effect and potential mechanism of  
12  
13 96 cerebellar vermis iTBS on balance in individuals with stroke since now. Preliminary pilot  
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15 97 study conducted by us found that cerebellar vermis iTBS contributed to increasing the  
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17 98 excitability of the bilateral supplementary motor areas (SMA) during balance tasks in healthy  
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19 99 adults.<sup>21</sup>  
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## 26 101 **Objective**

27  
28 102 A randomized controlled double-blind trial is conducted to determine the effects of cerebellar  
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30 103 vermis iTBS on trunk control, muscle activation and balance function in subacute stroke  
31  
32 104 patients since no clinical research have been reported to verify the effectiveness of cerebellar  
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34 105 vermis iTBS stimulation. We hypothesize that cerebellar vermis iTBS can promote the  
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36 106 activation of trunk and lower limbs muscles, and increase the excitability of SMA to improve  
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38 107 trunk control and balance function in patients with subacute stroke.  
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## 44 109 **Methods**

### 47 110 **Study design and setting**

48  
49 111 This study is a prospective single-center double-blind randomized controlled clinical trial  
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51 112 with 3-week intervention and 3-week follow-up. The protocol is strictly followed the standard  
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53 113 protocol guidelines: SPIRIT 2013 Statement.<sup>22</sup> Eligible participants will be randomly  
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55 114 allocated in a 1:1 ratio to the experimental group or control group, respectively. After routine  
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57 115 conventional physical therapy, patients assigned to the experimental group will receive  
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3 116 cerebellar vermis iTBS whereas patients assigned to the control group will receive sham  
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5 117 stimulation. The overall intervention periods are five days a week for three consecutive  
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7 118 weeks. The outcomes will be measured at baseline (T0), 3 weeks post-intervention (T1), and  
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9 119 3 weeks follow-up (T3). The whole study will be performed at the Department of  
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11 120 Rehabilitation Medicine of Sichuan University West China Hospital (Chengdu, Sichuan  
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13 121 Province, China). Figure 1 shows the flow diagram of the study design. We plan to start  
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15 122 subject recruitment on the 15<sup>th</sup> of July 2022 and complete the trial in December 2024. Figure  
16  
17 123 2 illustrates the study schedule.  
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### 24 125 **Sample size calculation**

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26 126 The sample size calculation was conducted via G\*power of 3.1.9.2 based on the result of Berg  
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28 127 balance scale (BBS) score in our published study, which indicated an estimated effect size  $f$   
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30 128 =0.38.<sup>19</sup> Other parameters were set as follows: significance level  $\alpha=0.05$  (two tails), power  
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32 129  $(1-\beta)=90\%$ , correlation among repeated measures=0.5, nonsphericity correction  $\epsilon=1$ , number  
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34 130 of measurements=3, and number of groups=2. Therefore, the sample size of  $n=40$  was  
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36 131 obtained. After allowing for a 15% dropout rate, a minimum total of 46 participants are  
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38 132 needed.  
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### 45 134 **Participants**

#### 46 135 ***Recruitment***

47  
48 136 The participants will be recruited from the Department of Rehabilitation Medicine of Sichuan  
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50 137 University West China Hospital in Chengdu, Sichuan Province, China. After carefully  
51  
52 138 screening the inclusion and exclusion criteria, voluntary participants are required to provide  
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54 139 written informed consent before the experiment.  
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#### 58 140 ***Inclusion criteria***



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3 141 Participants will be considered for inclusion if they meet the following criteria:

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5 142 (1) A diagnosis of a stroke according to the *Diagnostic criteria of cerebrovascular diseases in*  
6  
7 143 *China (version 2019)*.<sup>23</sup>

8  
9  
10 144 (2) Aged between 18 and 65 years.

11  
12 145 (3) First-ever unilateral stroke confirmed by imaging examination.

13  
14 146 (4) Subacute stroke participants with the stroke onset ranged from 2 weeks to 6 months.<sup>18</sup>

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16  
17 147 (5) Having motor deficit and balance dysfunction, with the Fugl-Meyer assessment scale  
18  
19 148 score for lower extremities (FMA-LE) <34 points and BBS score <56 points.<sup>19</sup>

20  
21 149 ***Exclusion criteria***

22  
23  
24 150 Participants will be excluded if they meet any of the following criteria:

25  
26 151 (1) Diagnosis of coexisting other neurological diseases.

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28 152 (2) Injury of cerebellum or brain stem.

29  
30 153 (3) Having contraindications of iTBS (e.g., history of seizures, intracranial metallic implants,  
31  
32 154 microprocessor implants in the body, suffering from tumorous, and pregnancy)

33  
34 155 (4) Cognitive impairment with the mini-mental state examination (MMSE) score <27.

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40 157 **Interventions**

41  
42 158 All enrolled participants will receive 1 session of cerebellar vermis iTBS or sham stimulation  
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44 159 from Monday to Friday, always before routine conventional physical therapy, for a total of 15  
45  
46 160 sessions. The experimental group patients will receive cerebellar vermis iTBS coupled with  
47  
48 161 conventional physical therapy, and the control group patients will receive sham stimulation  
49  
50 162 coupled with conventional physical therapy. The whole intervention period will last three  
51  
52 163 consecutive weeks in total.

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58 165 ***Cerebellar vermis iTBS stimulation***

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3 166 The stimulation protocol will strictly adhere to the safety guidelines and recommendations  
4  
5 167 endorsed by the International Federation for Clinical Neurophysiology in 2021.<sup>24</sup> We will use  
6  
7 168 a Magstim Rapid2 stimulator (The Magstim Company Limited) connected to a 70 mm figure-  
8  
9  
10 169 of-8 Double Rapid2 Air Cooled Coil (P/N 3910-00) to stimulate the cerebellar vermis (Figure  
11  
12 170 3). The center of the coil will be placed tangentially to the target scalp and the coil current  
13  
14 171 direction will point downward. iTBS is applied over the cerebellar vermis, 1 cm inferior to the  
15  
16 172 inion.<sup>25</sup> We will use a neuronavigation system (BrainSightt, Rogue Research Inc.) coupled  
17  
18 173 with a Polaris Vicra infrared camera to ensure that cerebellar vermis iTBS is applied over the  
19  
20 174 same spot across different sessions in the same participant (Figure 3). The pattern of iTBS  
21  
22  
23 175 consists of 600 pulses containing 3 pulses at 50Hz repeated at a rate of 5Hz, with 20 trains of  
24  
25 176 10 bursts given at 8s intervals.<sup>26</sup> The standard stimulus intensity is set at 80% of the active  
26  
27 177 motor threshold (AMT), which is the lowest intensity evoking at least five out of ten motor-  
28  
29 178 evoked potentials (MEP) with a peak to peak amplitude >200  $\mu$ V in the abductor pollicis  
30  
31 179 brevis muscle during 10% of maximum voluntary contraction measuring by a dynamometer.<sup>20</sup>  
32  
33 180 If the participant cannot tolerate the preset standard stimulus intensity, the stimulator output  
34  
35 181 intensity is set to the participant's maximum tolerated intensity (MTI).<sup>27</sup>  
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41

### 42 183 ***Sham stimulation***

43  
44 184 In the control group, participants are treated identically except for using the Magstim's sham  
45  
46 185 coil (P/N 3950-00) to realize the sham stimulation.<sup>28</sup> The sham coil has the same external  
47  
48 186 appearance, parameters and application methods to simulate the sensation produced by the  
49  
50 187 real coil without induction of a magnetic field. Therefore, it can sufficiently ensure that the  
51  
52 188 patients remain blind to the intervention.  
53  
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55

### 56 189 57 58 190 ***Conventional physical therapy***

1  
2  
3 191 After receiving cerebellar vermis iTBS or sham stimulation, all participants will receive  
4  
5 192 conventional physical therapy, including limb positioning, balance exercise, trunk control,  
6  
7 193 postural and transfer training, lasting 50 min per session during intervention phase.  
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10 194

### 11 12 195 ***Discontinuing allocated interventions criteria***

13  
14 196 Participants will stop receiving any interventions if any of the following events occurs:

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16  
17 197 (1) Serious adverse events happen during the stimulation, such as epilepsy, severe headache,  
18  
19 198 persistent tinnitus and syncope.

20  
21 199 (2) Participants withdraw from the trial.

22  
23 200 (3) Participants are not compliant with the allocation and intervention plan.

24  
25 201 (4) Participants join in extra studies during the trial.

26  
27 202 (5) Group exposure for participants and outcomes evaluators lead to the failure of blindness.  
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30 203

### 31 32 33 204 ***Improving adherence strategies***

34  
35 205 In order to improve the participant compliance, the researcher in charge of the trial will

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37 206 contact the participants regularly to clarify the rehabilitation progress and discuss the

38  
39 207 subsequent physical therapy program. Additionally, patients who complete the entire

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41 208 procedure in accordance with the protocol are to be provided with a subject fee and an

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43 209 additional free rehabilitation consultation. Once the participant drops out, the specific reasons

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45 210 for withdrawal will be recorded.  
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### 49 50 51 212 **Outcome Measures**

52  
53 213 At the day of enrollment, the basic characteristics information of participants, including age,

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55 214 gender, type of stroke, lesion site, course of diseases, degree of neurological deficit assessed

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57 215 by National Institutes of Health Stroke Scale (NIHSS), and cognitive function assessed by  
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3 216 MMSE, are documented. The outcome assessments are performed at the treatments site before  
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5 217 intervention as a baseline (T0), after 3 weeks of intervention (T1) and after 3 weeks of follow-  
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7 218 up (T3). The primary outcomes are BBS and trunk impairment scale (TIS) scores. The  
8  
9 219 secondary outcomes are balance tests via the Balance Master system, muscle activation of  
10  
11 220 trunk and lower limbs via the surface electromyography (sEMG) recording, cerebral cortex  
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13 221 oxygen concentrations via the resting-state functional near-infrared spectroscopy (fNIRS),  
14  
15 222 FMA-LE scores, and Barthel index (BI) scores. Each assessment is performed by a  
16  
17 223 professional clinician or by a qualified physical therapist who is blinded to the experimental  
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19 224 condition of the participant.  
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### 23 225 *Primary outcomes*

#### 24 226 *1. BBS*

25  
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28 227 The BBS is a well-validated scale of balance among individuals with neurological disease.<sup>29</sup> It  
29  
30 228 has high reliability and internal validity, with the intraclass correlation coefficient (ICC) for  
31  
32 229 inter-measure reliability and intra-measure reliability is 0.97 and 0.98, respectively.<sup>30</sup> This  
33  
34 230 scale is a 14-item measure with a total score of 56, and the score of each item ranges from 0  
35  
36 231 (poor balance) to 4 (good balance).<sup>31</sup>  
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#### 40 232 *2. TIS*

41  
42 233 TIS is a scale designed to assess motor impairment of the trunk after stroke, illustrating the  
43  
44 234 most promising performance in psychometric properties with satisfactory reliability and  
45  
46 235 validity.<sup>32</sup> It is a 17-item scale with a total score rates from 0 to 23 points to evaluate static  
47  
48 236 and dynamic sitting balance and trunk coordination for stroke patients.<sup>33</sup> A higher score  
49  
50 237 indicates better trunk control.  
51  
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### 55 239 *Secondary outcomes*

#### 56 240 *1. balance tests via the Balance Master system*

241 The assessments of dynamic balance and postural control abilities are performed by sensory  
 242 organization test (SOT), limits of stability (LOS), and rhythmic weight shift (RWS) via the  
 243 Smart Equitest Balance Master System® (NeuroCom Int., Inc., Clackamas, Oregon, USA).  
 244 (Figure 4)

245 *1.1 SOT:* The SOT evaluates postural control when participants undergo different  
 246 somatosensory, visual, and vestibular feedback perturbations. When testing, inaccurate  
 247 interference information delivered to the patient's eyes, feet, and joints are controlled through  
 248 calibrated sway referencing of the support surface and/or visual surround. The participant is  
 249 required to maintain balance to keep their center of gravity (COG) as steady as possible. A  
 250 composite equilibrium score is provided to characterize the participant's overall level of  
 251 performance through six conditions described in Table 1. During SOT, each trial lasts for 20 s  
 252 and is repeated three times.<sup>34 35</sup>

**Table 1.** Sensory organization test

Condition	Vision	Surface	Surround	Interference
1	Eyes open	Stable	Fixed	Null
2	Eyes closed	Stable	Fixed	Vision
3	Eyes open	Stable	Unfixed	Vision
4	Eyes open	Unstable	Fixed	Somatosensation
5	Eyes closed	Unstable	Fixed	Somatosensation and Vision
6	Eyes open	Unstable	Unfixed	Somatosensation and Vision

253

254 *1.2 LOS:* The LOS quantifies the voluntary ability to shift the COG towards eight different  
 255 directions, which are forward, forward-right, right, backward-right, backward, backward-left,  
 256 left, and forward -left. When the test is performed, a real-time display of their COG position  
 257 in relation to targets placed at the center of the base of support and the stability limits is  
 258 shown. Once the command is given, the participant needs to move the COG as quickly (up to  
 259 8 seconds) and accurately as possible from a central position out towards one of eight

1  
2  
3 260 targets.<sup>36</sup>  
4

5 261 *1.3 RWS*: The RWS evaluates the participant's ability to perform rhythmic movements of  
6  
7 262 their COG moves from left to right (lateral) and forward to backward (anterior/posterior)  
8  
9 263 between two targets at three different speeds (slow, medium and fast).<sup>37</sup> Movement velocity  
10  
11 264 and directional control are measured in each direction and speed.  
12  
13  
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15 265

## 16 17 266 **2. sEMG recordings**

18  
19 267 The sEMG recordings will be conducted in accordance with SENIAM guidelines.<sup>38</sup> A 20-  
20  
21 268 channel wireless BTS-FREEEMG 300 (BTS Biomechanics Ltd, Italy) is used to collect the  
22  
23 269 sEMG signals of the following muscles: bilateral rectus abdominis (RA), external oblique  
24  
25 270 muscle (EO), erector spinae (longissimus), rectus femoris (RF), biceps femoris (BF), tibialis  
26  
27 271 anterior (TA) and soleus (Table 2 and Figure 5 illustrate the sensor locations on individual  
28  
29 272 muscles). Before starting, the skin should be cleaned using 75% alcohol and would be shaved  
30  
31 273 if needed to ensure a maximum skin impedance below 5k $\Omega$ . After skin preparation, the  
32  
33 274 participant has to be placed in the starting posture that depends on the muscle at which the  
34  
35 275 electrodes will be placed. A pair of pre-gelled electrodes certified for a medical use and  
36  
37 276 complying with the directive 93/42/EEC (amended by 2007/47/EC) are placed on the belly of  
38  
39 277 the target muscle with an interelectrode distance of 2 cm.<sup>39</sup> When the electrodes are placed  
40  
41 278 and fixed, a certified physical therapist will teach the patient to perform the maximum  
42  
43 279 voluntary isometric contraction (MVIC) of the target muscle. For individual muscles, we will  
44  
45 280 record three 3s trails of MVIC with a 2min rest between each trail.  
46  
47 281 sEMG signals are sampled at 1000 Hz. Collected data are synchronously transmitted to a BTS  
48  
49 282 EMG-Analyzer (BTS Bioengineering) with the band-pass filtered from 20 to 500Hz. We will  
50  
51 283 rectify and filter the recorded signal and extract the data of averaged electromyography  
52  
53 284 (AEMG), root mean square (RMS), mean power frequency (MPF) and median frequency  
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285 (MF) for subsequent analyses.

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**Table 2.** The sensor locations of sEMG on individual muscles\*

Muscle	Starting posture of participant	Electrode placement	
		Location	Orientation
RA	Supine or standing	At 2cm superior and 2-4cm lateral to the umbilicus	Vertical
EO	Supine or standing	At 2 finger width above the anterior half of the iliac crest	In the direction of the line from the outside of the 5-12 ribs to the anterior half of the iliac crest
longissimus	Prone with the lumbar vertebral columns slightly flexed	At 2 finger width lateral from the proc. spin. of L1.	Vertical
RF	Sitting on a table with the knees in slight flexion and the upper body slightly bend backward	At 50% on the line from the anterior spina iliaca superior to the superior part of the patella	In the direction of the line from the anterior spina iliaca superior to the superior part of the patella
BF	Lying on the belly with the face down with the thigh down on the table and the knees flexed (to less than 90 degrees) with the thigh in slight lateral rotation and the leg in slight lateral rotation with respect to the thigh	At 50% on the line between the ischial tuberosity and the lateral epicondyle of the tibia	In the direction of the line between the ischial tuberosity and the lateral epicondyle of the tibia
TA	Supine or sitting	At 1/3 on the line between the tip of the fibula and the tip of the medial malleolus	In the direction of the line between the tip of the fibula and the tip of the medial malleolus



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soleus	Sitting with the knee approximately 90 degrees flexed and the heel / foot of the investigated leg on the floor	At 2/3 of the line between the medial condylis of the femur to the medial malleolus	In the direction of the line between the medial condylis to the medial malleolus
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Abbreviations: sEMG, surface electromyography; RA, rectus abdominis; EO, external oblique muscle; RF, rectus femoris; BF, biceps femoris; TA, tibialis anterior.

\* According to the SENIAM recommendations for sensor locations for muscles.

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### 289 **3. *resting-state fNIRS***

290 A multichannel fNIRS system with 24 sources and 24 detectors (NirScan, HuiChuang, China)  
291 will be used to record changes of oxygenated hemoglobin (HbO<sub>2</sub>), deoxygenated Hb and total  
292 Hb of the cerebral cortex when the participant is at rest. Relevant parameters are set as  
293 follows: the wavelengths are between 730 and 850 nm, the source-detector distance is 3 cm,  
294 and the sampling frequency is over 11Hz. The international 10/20 system is referenced for  
295 identifying optodes on the bilateral prefrontal and parietal lobes.<sup>40</sup> Collected fNIRS data are  
296 analyzed by the NirSpark software package with the band-pass filtered from 0.01 to 0.1 Hz.  
297 Extract the mean HbO<sub>2</sub> value of each channel for statistical analyses.

### 299 **4. *FMA-LE***

300 The lower extremity function of stroke patients is assessed by FMA-LE, which has good  
301 interrater reliability and concurrent validity.<sup>41</sup> The maximum score of this 17-item scale is 34.  
302 Each item is scored on a 3-point ordinal scale, with 0 for inability, 1 for partial ability, and 2  
303 for full ability to perform the required movement.<sup>42</sup>

### 305 **5. *BI***

306 The BI is a self-reported scale comprised of 10 items, including bathing, grooming, bladder  
307 management, bowel management, dressing, feeding, toilet use, transfers, ascending and  
308 descending stairs, and walking, to measure the basic activities of daily living (ADL).<sup>43</sup> The  
309 total scores vary from 0 (totally dependent) to 100 (independent). This scale has good  
310 clinimetric properties and excellent inter-rater reliability with standardized administration in  
311 stroke patients.<sup>18 44</sup>

### 313 ***Safety measurement***

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3 314 Possible stimulation-related adverse events, such as headache, nausea, neck pain, seizure,  
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5 315 mood changes, fatigue, tinnitus, dizziness, sleepiness and syncope, are listed in the informed  
6  
7 316 consent. An adverse reaction record is used to monitor and report in detail after each  
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9 317 stimulation. In addition, any adverse events related to in conventional physical therapy will be  
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11 318 also recorded using the adverse event case report form (CRF).  
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## 16 17 320 **Randomization and blinding**

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19 321 The study is a randomized, double-blind, sham-controlled trial. Enrolled participants are  
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21 322 randomly signed based on the computer-generated random numbers that are concealed in  
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23 323 opaque numbered envelopes and opened in numerical order by a neutral non-involved  
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25 324 researcher. We plan to blind the participants and evaluators. Once blinding fails, the  
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27 325 participant will be removed. The sham coil is used to ensure the patients are blinded to the  
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29 326 intervention. Outcome evaluations will be conducted by a professional clinician or by a  
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31 327 qualified physical therapist who is blinded to the group assignment. An independent  
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33 328 researcher is designated to complete the data analysis. Unblinding will be carried out after the  
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35 329 data analysis is completed. In case of serious adverse events happen during interventions,  
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37 330 emergency unblinding will be also implemented.  
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## 43 44 332 **Data management and analysis**

### 45 46 333 *Data management*

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48 334 Data will be recorded on CRFs in a timely, complete and accurate manner. Two researchers  
49  
50 335 independently input data into the Excel software of computer and proofread each other. Thus,  
51  
52 336 electronic data will be stored and available by the relevant researcher only. The West China  
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54 337 Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University are  
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56 338 responsible for monitoring the safety and process of the study and has the right to terminate  
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3 339 the trial if serious adverse events happened. All procedures will comply with the  
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5 340 confidentiality standards for medical data.  
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10 342 ***Statistical analysis***

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12 343 Statistical analyses will be performed using GraphPad Prism 8.4.3 (GraphPad Software, Inc.,  
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14 344 La Jolla, CA, USA) based on the Intention-To-Treat (ITT) principle. Missing data are  
15  
16 345 imputed using the last observation carried forward approach. The Shapiro-Wilk test is  
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18 346 conducted to evaluate the normal distribution of data. The level of significance is set at  $\alpha =$   
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20 347 0.05. Continuous variables, ordinal variables, and categorical variables are presented as mean  
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22 348 ( $\pm$ standard deviation, SD), medians (interquartile range, IQR), and number (percentage, %),  
23  
24 349 respectively. Based on different types of data, the independent-samples *t* test, Mann–Whitney  
25  
26 350 U test, and chi-square test are used to compare the demographic and baseline data between  
27  
28 351 groups. The two-way mixed measures analysis of variance (ANOVA) with group as a  
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30 352 between-individual factor and time as a within-individual factor is performed for outcome  
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32 353 measures analyses. Nonsphericity correction is conducted using the Greenhouse-Geisser  
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34 354 correction if necessary, and Tukey's *post hoc* multiple comparison test is applied.  
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42 356 ***Patient and public involvement***

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44 357 Patients and the public are not involved in the study design, recruitment, implementation or  
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46 358 report. However, the study results will be disseminated to the public through academic papers  
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48 359 and conferences.  
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53 361 **Ethical approval, trial registration and dissemination**

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55 362 The study was approved by the West China Hospital Clinical Trials and Biomedical Ethics  
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57 363 Committee of Sichuan University on May 19, 2022 (ethics reference: 2022 (573)), and will be  
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3 364 conducted in accordance with the Declaration of Helsinki.  
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5 365 This protocol was registered on June 16, 2022, in the Chinese Clinical Trial Registry with the  
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7 366 registration number is ChiCTR2200061225. All participants will be fully informed of the  
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10 367 study procedures and sign the informed consent voluntarily before inclusion (see Appendix).  
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12 368 The private information of all participants will be kept confidential through securing in a  
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14 369 locked cabinet and only accessible to researchers of the study. However, the results of this  
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16 370 study will be published in peer-reviewed journals and disseminated in academic conferences.  
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## 21 372 **Discussion**

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24 373 At present, there is no research has revealed the effect and potential mechanism of cerebellar  
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26 374 vermis iTBS stimulation on balance in subacute stroke patients. This prospective single-center  
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28 375 double-blind randomized controlled clinical trial with 3-week intervention and 3-week  
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30 376 follow-up is designed to confirm its effectiveness.  
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33 377 Our study will comprehensively assess the trunk control and balance function by clinical  
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35 378 scales, balance tests via the Smart Equitest Balance Master System and sEMG measurements.  
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38 379 Additionally, we will also collect the concentration of HbO<sub>2</sub> in cerebral cortex via the resting-  
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40 380 state fNIRS. Integrated data results sufficiently verify the research hypothesis.  
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43 381 For trunk control, the scores of TIS reveal the motor impairment of the trunk for stroke  
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45 382 patients. sEMG signal reflects the activation of muscles directly and contains information  
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47 383 about movement intention generated by the brain.<sup>45</sup> AEMG represents the degree of muscle  
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49 384 activation and the synchronization of activated motor units. RMS quantifies the effort of the  
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51 385 muscle. MPF and MF are kinds of frequency domain features and indicate muscle fatigue.<sup>46 47</sup>  
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54 386 For balance function, the scores of BBS reflect the overall performance of static and dynamic  
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56 387 balance. Accurate integration of sensory information is critical to maintaining balance. The  
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58 388 composite equilibrium score of SOT characterizes the impairments of individual sensory  
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3 389 systems.<sup>48</sup> Ability to voluntarily move the COG within the LOS is fundamental to mobility  
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5 390 tasks. By LOS test, reaction time, movement velocities and excursions are recorded to  
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7 391 measure the voluntary ability to shift the COG without losing balance. Reaction time reflects  
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9 392 the ability of cognitive processing. Movement velocities indicate the high-level central  
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11 393 nervous system function. Excursions can be restricted by biomechanical deficits.<sup>49</sup> Overall,  
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13 394 limitations in the LOS are associated with instability during weight-shifting activities. RWS  
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15 395 measures movement velocity and directional control during rhythmic movements. Rhythmic,  
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17 396 reciprocal movement patterns are required in daily activities. Stroke patients with disrupted  
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19 397 normal rhythmic movement control are exhibit reduced velocities and/or poor directional  
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21 398 control ability.<sup>50</sup>  
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24 399 For cortical activation, fNIRS is a widespread non-invasive measurement which provides  
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26 400 real-time monitoring hemodynamic signals to reflect the changes of brain activation.<sup>51</sup>  
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28 401 Increased HbO<sub>2</sub> is positively correlated with cortical excitability. Besides, balance function  
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30 402 and postural stability are positively related to the changes of HbO<sub>2</sub> signals in the bilateral  
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32 403 SMA in stroke patients.<sup>52</sup> Additionally, our previous work have revealed single-session  
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34 404 cerebellar vermis iTBS can increase the bilateral SMA excitability during the balance tasks in  
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36 405 healthy adults.<sup>21</sup>  
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38 406 We hypothesize that cerebellar vermis iTBS can promote the activation of muscles in trunk  
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40 407 and lower limbs, and increase the excitability of SMA to improve trunk control and balance  
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42 408 function in patients after stroke. Cerebellar vermis plays an important role in balance and  
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44 409 motor control. SMA contributes to anticipatory postural adjustments and postural stability  
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46 410 during gait initiation.<sup>53</sup> iTBS consists of high-frequency stimulation bursts to strongly  
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48 411 modulate the neural activity of cerebellar vermis. Given that studies in humans have shown  
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50 412 iTBS drives acute changes to motor behavior and neuronal excitability.<sup>54</sup> The possible  
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52 413 mechanism has been reported by an animal study that iTBS can promote neural structural  
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3 414 remodeling and functional recovery by enhancing neurogenesis and migration via miR-551b-  
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5 415 5p/BDNF/TrkB pathway.<sup>55</sup> The study of cerebellar vermis stimulation was first reported in  
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7 416 1995, which investigated its effects on saccade metrics in man via TMS.<sup>56</sup> At present,  
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9 417 researchers reported that cerebellar vermis is a safe and well-tolerated brain stimulation  
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11 418 technology having a potential therapeutic effect on schizophrenia.<sup>57</sup> In addition, cerebellar  
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13 419 vermis rTMS can induce a suppressive effect on pharyngeal motor cortical activity and  
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15 420 swallowing behavior.<sup>58</sup> However, limited researches have reported that cerebellar vermis  
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17 421 plays an important role in postural response and balance stability.<sup>13 59</sup> Therefore, we hopefully  
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19 422 identify the effectiveness of cerebellar vermis iTBS in trunk control and balance function for  
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21 423 subacute stroke individuals. Our results may provide valuable information to develop a novel  
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23 424 treatment method for the rehabilitation of balance dysfunction after stroke.  
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31 426 **Author contributions:** Conceptualization, validation, and original draft: YC.  
32  
33 427 Recruitment: LH, HHJ, and QCW. Data collection: YC, WS, and HXT. Data analysis: CFG  
34  
35 428 and QFG. Manuscript review and editing: CFG and QG. QG designed the trial and was  
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37 429 responsible for the manuscript. All authors read and approved the final manuscript.  
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3 656 **Legends**  
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6 657 **Figure 1.** The flow diagram of the study design.  
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8 658 **Figure 2.** The schedule of enrolment, interventions, and assessments.  
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10 659 **Figure 3.** The Magstim Rapid2 stimulator with a BrainSight neuronavigation system.  
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12 660 **Figure 4.** The Smart Equitest Balance Master System®.  
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14 661 **Figure 5.** The sensor locations on individual muscles for sEMG recording (A. rectus  
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17 662 abdominis, B. external oblique muscle, C. rector spinae (longissimus), D. rectus femoris, E.  
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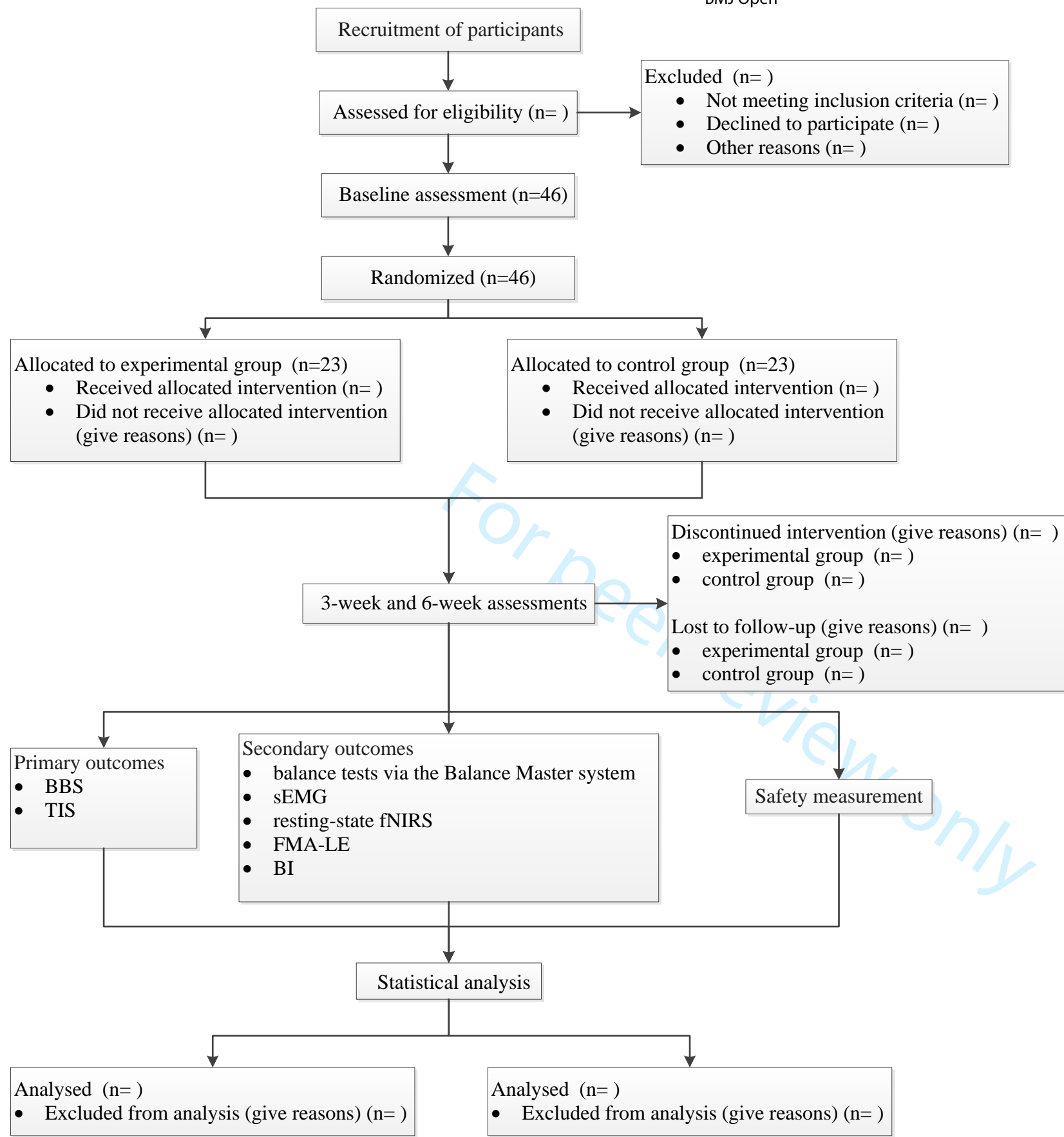
19 663 biceps femoris, F. tibialis anterior, G. soleus  
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**Enrollment**

**Intervention**

**Assessment**

**Analysis**





**Figure 2.** The schedule of enrolment, interventions, and assessments.

	<b>Enrolment</b>	<b>Allocation</b>	<b>Post-allocation</b>					
<b>TIMEPOINT</b>	<b>-t<sub>1</sub></b>	<b>0</b>	<b>W1</b>	<b>W2</b>	<b>W3</b>	<b>W4</b>	<b>W5</b>	<b>W6</b>
<b>ENROLMENT:</b>								
Eligibility screen	X							
Informed consent	X							
Ethical approval and trial registration	X							
Allocation		X						
<b>INTERVENTIONS:</b>								
cerebellar vermis iTBS and conventional physical therapy			←————→					
sham stimulation and conventional physical therapy			←————→					
<b>ASSESSMENTS:</b>								
basic characteristics information		X						
BBS		X			X			X
TIS		X			X			X
balance tests via the Balance Master system		X			X			X
sEMG		X			X			X
resting-state fNIRS		X			X			X
FMA-LE		X			X			X
BI		X			X			X
Safety measurement			X	X	X	X	X	X

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4 W, week; iTBS, intermittent theta-burst stimulation; BBS, Berg balance scale; TIS,  
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6 trunk impairment scale; sEMG, surface electromyography; fNIRS, functional near-  
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8 infrared spectroscopy; FMA-LE, Fugl-Meyer assessment scale score for lower  
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10 extremities; BI, Barthel index.  
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For peer review only

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Figure 3. The Magstim Rapid2 stimulator with a BrainSight neuronavigation system.

1066x1422mm (72 x 72 DPI)



Figure 4. The Smart Equitest Balance Master System®.

1066x1422mm (72 x 72 DPI)

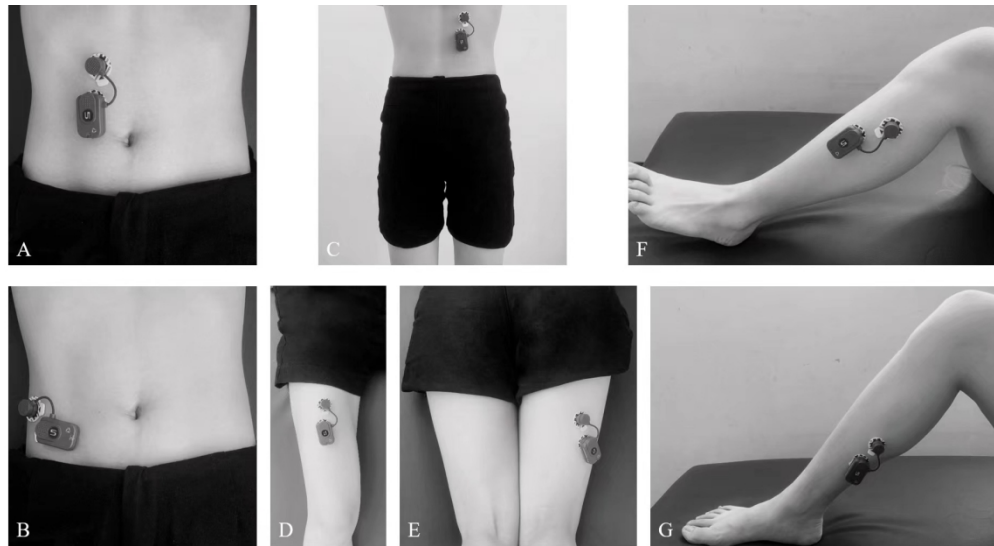


Figure 5. The sensor locations on individual muscles for sEMG recording (A. rectus abdominis, B. external oblique muscle, C. rector spinae (longissimus), D. rectus femoris, E. biceps femoris, F. tibialis anterior, G. soleus)

654x359mm (72 x 72 DPI)

**Appendix.** Informed Consent Form

<b>West China Hospital, Sichuan University</b>			
<b>Participant Informed Consent</b>			
<b>Name:</b>	<b>Gender:</b>	<b>Age:</b>	<b>Inpatient ID:</b>
<p><b>Title of study:</b> The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for subacute stroke patients: a randomized controlled trial</p> <p><b>Investigator:</b> Qiang Gao</p> <p><b>Funding:</b> NSFC 82172540 from the National Natural Science Foundation of China</p> <p><b><i>What is the study about?</i></b></p> <p>The aim of the study is to determine the effects of cerebellar vermis intermittent theta-burst stimulation (iTBS) on trunk control, muscle activation and balance function in stroke patients. We will recruit 46 patients who meet the inclusion criteria as follows: (1) a diagnosis of a stroke according to the Diagnostic criteria of cerebrovascular diseases in China (version 2019), (2) aged between 18 and 65 years, (3) first-ever unilateral stroke confirmed by imaging examination, (4) subacute stroke participants with the stroke onset ranged from 2 weeks to 6 months, (5) having motor deficit and balance dysfunction, with the Fugl-Meyer assessment scale score for lower extremities (FMA-LE) &lt;34 points and BBS score &lt;56 points. Patients were excluded if they presented one of the following: (1) coexisting other neurological diseases, (2) injury of cerebellar or brain stem, (3) having contraindications of iTBS (e.g., history of seizures, intracranial metallic implants, microprocessor implants in the body, suffering from tumorous, and pregnancy), (4) cognitive impairment with the mini-mental state examination (MMSE) score &lt;27.</p> <p><b><i>How long will I be in the study?</i></b></p> <p>Your part in the study will last <b>6 weeks</b> with 3 weeks of intervention and 3 weeks of follow-up (excluding assessment).</p>			

***What will happen in this study?***

You will be randomized into either the experimental or control group according to the random number table. If you assigned to the experimental group will receive cerebellar vermis iTBS after routine daily conventional physical therapy, otherwise you will receive sham stimulation after routine daily conventional physical therapy. The overall intervention periods are five days a week for three consecutive weeks. You will be assessed before treatment, after 3 weeks of intervention and after 3 weeks of follow-up. The measures including clinical scales, balance tests via the Balance Master system, and the surface electromyography recording.

If you are eligible and wish to join the study, you must sign this consent form. If you do not sign the consent form you cannot join the study.

We will review this consent form with you. You will be given enough time to review the consent and have all your questions about the study answered. We will give you a signed copy of the consent for your records before treatment in person.

Study staff will not know which group or study treatment you are assigned to. You should not join the study if you are not willing to take the study treatment (or join the group) you are assigned to.

***What if I have questions?***

You can contact the therapist at working hours if you have questions about the study. Qiang Gao (the director of therapists) is in charge of the study.

***Do I have to be in the study?***

You decide if you want to be in the study. Deciding not to take part will not affect your relationship with your therapist. If your therapist is an investigator for the



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4 study, you may get a second opinion from another therapist not involved in the  
5 study.  
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9 You can leave the study at any time and you do not have to give a reason. Leaving  
10 the study will not affect your relationship with your therapist.  
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15 The study investigators may ask you to leave the study if it is in your best interest.

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17 The study investigator may ask you to leave the study if you do not follow the study  
18 rules.  
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23 ***What if I don't want to be in the study?***  
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25 You can choose not to be in the study and you do not have to give a reason. You can  
26 choose to (talk to your doctor/therapist about other options, investigate outside  
27 resources on your own, etc.).  
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33 ***Are there any costs?***  
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35 All study-related treatments are free.  
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39 ***Will I be paid for being in the study?***  
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41 You will not be paid for being in the study.  
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45 ***Are there any risks?***  
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47 There is always a small risk of a breach of confidentiality to your personal health  
48 information. However, these risks have been addressed and minimized as much as  
49 is possible.  
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54 You will be told about any new information that may affect your willingness to  
55 participate in the study.  
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4 There are some possible risks and side effects as follows: headache, nausea, neck  
5 pain, seizure, mood changes, fatigue, tinnitus, dizziness, sleepiness and syncope.  
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9 If you experience any side effects while on the study contact investigator (Qiang  
10 Gao) at any time as soon as possible.  
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15 ***What if I feel I've been hurt by taking part in the study?***  
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17 If you feel you have been injured or harmed by taking part in this study, please  
18 contact investigator (Qiang Gao) at any time. If you feel you were harmed while  
19 taking part in this study, you may be treated at West China Hospital, Sichuan  
20 University. However, West China Hospital does not offer to pay the cost of this  
21 treatment.  
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29 If you feel your rights have been violated or you have harmed by this study, please  
30 contact your therapist.  
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35 ***Are there any benefits?***  
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37 It is possible you may receive some benefit from cerebellar vermis iTBS and  
38 conventional physical therapy. iTBS is a novel form of rTMS, which can produce  
39 long-term potentiation and is more rapid and efficacious than standard rTMS.  
40 Cerebellar vermis is a cardinal structure involved in balance and motor control,  
41 which is responsible for regulating the trunk, head, neck and proximal limb muscles  
42 to control posture and maintain balance. There is no guarantee, however, that you  
43 will receive any benefit at all. Your participation will help us learn more about the  
44 effects of cerebellar vermis iTBS on trunk control, muscle activation and balance  
45 function in subacute stroke patients.  
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56 ***Your privacy is important***  
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58 Protecting your privacy is very important to us.  
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During this study we will ask about your (past) and (current) medical history. This information will be used to determine your eligibility for the study and provide data for the study. Your personal health information will be kept private and only authorized study staff will have access to this information. We will use a study number instead of your name. All paper forms will be kept in a locked, secure office. All electronic data will be stored on password-protected computers. Your name will not be used in any publications or presentations about this study.

During the study, you may not be given access to medical information about you that is part of the study. When the study is over, you may request certain medical information collected about you that is part of your study medical record.

None of your personal information will be shared outside of West China Hospital.

By signing this consent form, you are stating that we can use your health information in the ways mentioned above for this study. You are not waiving any of your legal right by signing this form.

You have the right to take away your permission to use your health information collected as part of the study. In order to do this, you must send a written request to: Qiang Gao, department of rehabilitation, West China hospital, Sichuan University

Once your letter is received, no additional information about you will be collected from you for this study. Any data that were collected before we receive your letter will continue to be used for the study. Taking away your permission to use your health information will not affect your relationship with West China Hospital.

We are collecting only the personal health information that we need for the specific

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4 purpose of this study. Your personal health information cannot be used for  
5 additional research purpose.  
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9 The West China hospital may be required to provide copies of your personal  
10 information to government agencies as required by law.  
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15 Your permission to use your identifiable health information when the study is  
16 complete.  
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19 ***Signatures:***

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21 By signing this consent form, it means the following:  
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- 23 ● I know my rights have not been waived by signing.
- 24 ● I have had all of my questions answered and I know whom to ask if I have more  
25 questions.  
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- 27 ● I have read this form and understand it.
- 28 ● I want to join the study.
- 29 ● I know I can leave the study at any time and do not have to give a reason.  
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39 Signature of Participant

\_\_\_\_\_ Date



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

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Section/item	Item No	Description	Page
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 17-18
	2b	All items from the World Health Organization Trial Registration Data Set	nil
Protocol version	3	Date and version identifier	nil
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, 20
	5b	Name and contact information for the trial sponsor	Title page
	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	20
	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)	nil
<b>Introduction</b>			
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	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4

## Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6-7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5, Fig.2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5-6

## Methods: Assignment of interventions (for controlled trials)

Allocation:

1	Sequence	16a	Method of generating the allocation sequence (eg,	16
2	generation		computer-generated random numbers), and list of any	
3			factors for stratification. To reduce predictability of a random	
4			sequence, details of any planned restriction (eg, blocking)	
5			should be provided in a separate document that is	
6			unavailable to those who enrol participants or assign	
7			interventions	
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg,	16
11	concealment		central telephone; sequentially numbered, opaque, sealed	
12	mechanism		envelopes), describing any steps to conceal the sequence	
13			until interventions are assigned	
14				
15	Implementation	16c	Who will generate the allocation sequence, who will enrol	16
16			participants, and who will assign participants to interventions	
17				
18				
19	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg,	16
20			trial participants, care providers, outcome assessors, data	
21			analysts), and how	
22				
23		17b	If blinded, circumstances under which unblinding is	16
24			permissible, and procedure for revealing a participant's	
25			allocated intervention during the trial	
26				
27				
28	<b>Methods: Data collection, management, and analysis</b>			
29				
30	Data collection	18a	Plans for assessment and collection of outcome, baseline,	16
31	methods		and other trial data, including any related processes to	
32			promote data quality (eg, duplicate measurements, training	
33			of assessors) and a description of study instruments (eg,	
34			questionnaires, laboratory tests) along with their reliability	
35			and validity, if known. Reference to where data collection	
36			forms can be found, if not in the protocol	
37				
38				
39		18b	Plans to promote participant retention and complete follow-	16-17
40			up, including list of any outcome data to be collected for	
41			participants who discontinue or deviate from intervention	
42			protocols	
43				
44				
45	Data management	19	Plans for data entry, coding, security, and storage, including	16
46			any related processes to promote data quality (eg, double	
47			data entry; range checks for data values). Reference to	
48			where details of data management procedures can be	
49			found, if not in the protocol	
50				
51				
52	Statistical methods	20a	Statistical methods for analysing primary and secondary	17
53			outcomes. Reference to where other details of the statistical	
54			analysis plan can be found, if not in the protocol	
55				
56		20b	Methods for any additional analyses (eg, subgroup and	17
57			adjusted analyses)	
58				
59				
60				

1		20c	Definition of analysis population relating to protocol non-	17
2			adherence (eg, as randomised analysis), and any statistical	
3			methods to handle missing data (eg, multiple imputation)	
4				
5	<b>Methods: Monitoring</b>			
6				
7	Data monitoring	21a	Composition of data monitoring committee (DMC); summary	16
8			of its role and reporting structure; statement of whether it is	
9			independent from the sponsor and competing interests; and	
10			reference to where further details about its charter can be	
11			found, if not in the protocol. Alternatively, an explanation of	
12			why a DMC is not needed	
13				
14				
15		21b	Description of any interim analyses and stopping guidelines,	16
16			including who will have access to these interim results and	
17			make the final decision to terminate the trial	
18				
19	Harms	22	Plans for collecting, assessing, reporting, and managing	15-16
20			solicited and spontaneously reported adverse events and	
21			other unintended effects of trial interventions or trial conduct	
22				
23				
24	Auditing	23	Frequency and procedures for auditing trial conduct, if any,	16
25			and whether the process will be independent from	
26			investigators and the sponsor	
27				
28				
29	<b>Ethics and dissemination</b>			
30				
31	Research ethics	24	Plans for seeking research ethics committee/institutional	17-18
32	approval		review board (REC/IRB) approval	
33				
34	Protocol	25	Plans for communicating important protocol modifications	nil
35	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
36			relevant parties (eg, investigators, REC/IRBs, trial	
37			participants, trial registries, journals, regulators)	
38				
39				
40	Consent or assent	26a	Who will obtain informed consent or assent from potential	18
41			trial participants or authorised surrogates, and how (see	
42			Item 32)	
43				
44		26b	Additional consent provisions for collection and use of	not applicable
45			participant data and biological specimens in ancillary	
46			studies, if applicable	
47				
48				
49	Confidentiality	27	How personal information about potential and enrolled	18
50			participants will be collected, shared, and maintained in	
51			order to protect confidentiality before, during, and after the	
52			trial	
53				
54	Declaration of	28	Financial and other competing interests for principal	20
55	interests		investigators for the overall trial and each study site	
56				
57				
58	Access to data	29	Statement of who will have access to the final trial dataset,	16
59			and disclosure of contractual agreements that limit such	
60			access for investigators	

1	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	nil
2				
3				
4				
5	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
6				
7				
8				
9				
10				
11				
12		31b	Authorship eligibility guidelines and any intended use of professional writers	nil
13				
14				
15		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	nil
16				
17				
18				
19	<b>Appendices</b>			
20				
21	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
22				
23				
24	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	not applicable
25				
26				
27				
28				

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.



# BMJ Open

## The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for subacute stroke patients: a randomized controlled trial protocol

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SCHOLARONE™  
Manuscripts

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4 1 **The effectiveness of cerebellar vermis intermittent theta burst**  
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7 2 **stimulation in improving trunk control and balance function for**  
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10 3 **subacute stroke patients: a randomized controlled trial protocol**  
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## 17 **Abstract**

18 **Introduction** Balance impairments frequently occur in stroke patients. Achieving effective  
19 core trunk stability is the key to improving balance ability. However, there is still a lack of  
20 advanced well-defined rehabilitation protocols for balance improvement in stroke patients.  
21 Intermittent theta-burst stimulation (iTBS) is a noninvasive brain activity modulation strategy  
22 that can produce long-term potentiation. The cerebellar vermis is a fundamental structure  
23 involved in balance and motor control. However, no study has demonstrated the therapeutic  
24 effect and potential mechanism of cerebellar vermis iTBS on balance in individuals with  
25 stroke.

26 **Methods and Analysis** This study will be a prospective single-centre double-blind  
27 randomized controlled clinical trial with a 3-week intervention and 3-week follow-up.  
28 Eligible participants will be randomly allocated to the experimental group or the control  
29 group in a 1:1 ratio. After routine conventional physical therapy, patients in the experimental  
30 group will receive cerebellar vermis iTBS, whereas patients in the control group will receive  
31 sham stimulation. The overall intervention period will be five days a week for three  
32 consecutive weeks. The outcomes will be measured at baseline (T0), 3 weeks postintervention  
33 (T1) and at the 3-week follow-up (T3). The primary outcomes are Berg Balance Scale (BBS)  
34 and Trunk Impairment Scale (TIS) scores. The secondary outcomes are balance tests scores  
35 via the Balance Master system, muscle activation of the trunk and lower limbs via the surface  
36 electromyography (sEMG) recordings, cerebral cortex oxygen concentrations measured via  
37 the resting-state functional near-infrared spectroscopy (fNIRS), and Fugl-Meyer Assessment  
38 of Lower Extremity (FMA-LE) and Barthel index (BI) scores.

39 **Ethics and Dissemination** This study was approved by the West China Hospital Clinical  
40 Trials and Biomedical Ethics Committee of Sichuan University. The trial registration number

1  
2  
3 41 is ChiCTR2200065369. All participants will sign the informed consent form voluntarily. The  
4  
5 42 results of this study will be published in peer-reviewed journals and disseminated at academic  
6  
7 43 conferences.  
8  
9

10 44

## 11 12 13 45 **Strengths and limitations of this study**

- 14  
15 46 ➤ Our study comprehensively assesses the trunk control and balance function by clinical  
16  
17 47 scales, balance tests via the Smart Equitest Balance Master System, and surface  
18  
19 48 electromyography (sEMG) measurements.
- 20 49 ➤ Resting-state functional near-infrared spectroscopy (fNIRS) will be used to collect the  
21  
22 50 concentration of HbO<sub>2</sub> in the cerebral cortex.
- 23  
24 51 ➤ This study lacks a long-term follow-up assessment.  
25  
26  
27  
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30 52

## 31 32 53 **Introduction**

33  
34 54 Stroke is the third most common cause of disability worldwide.<sup>1</sup> The incidents, prevalence,  
35  
36 55 and disability-adjusted life-years of stroke have increased over the past two decades<sup>2</sup>, and are  
37  
38 56 considered to place heavy economic burdens on society. Balance impairments frequently  
39  
40 57 occur in patients with stroke, with a reported incidence ranging from 61% to 83%<sup>3</sup>. The main  
41  
42 58 manifestations are postural instability, weak trunk control, and difficulty shifting weight,<sup>4</sup>  
43  
44 59 which ultimately result in falls, poor mobility, decreased physical activity, and reduced  
45  
46 60 quality of life in patients.<sup>5</sup> Therefore, improvement of balance function is a cardinal  
47  
48 61 requirement in patients with stroke.  
49  
50

51  
52  
53 62 The trunk plays a fundamental role in trunk control, balance, and mobility during sitting and  
54  
55 63 transferring.<sup>6</sup> The synchronized activity of trunk muscles is necessary for maintaining  
56  
57 64 dynamic balance. In addition, proper trunk muscle control is essential for stabilizing distal  
58  
59  
60

1  
2  
3 65 limbs.<sup>7</sup> Muscle weakness of the lower limbs is associated with decreased standing balance  
4  
5 66 control.<sup>8</sup> Impaired trunk control and core muscle weakness attenuate balance and physical  
6  
7 67 function in individuals after stroke.<sup>9</sup> Therefore, achieving effective core trunk stability is  
8  
9 68 crucial to improving balance ability after stroke.

10  
11  
12 69 The cerebellum, a central brain structure located in the posterior cranial fossa, works in  
13  
14 70 concert with the cerebral cortex, brainstem, and spinal cord and is involved in motor control.<sup>10</sup>

15  
16  
17 71 <sup>11</sup> It consists of two lateral hemispheres and the cerebellar vermis. The cerebellar vermis is a  
18  
19 72 fundamental structure involved in balance and motor processing,<sup>12 13</sup> and is responsible for  
20  
21 73 regulating the trunk, head, neck and proximal limb muscles to control posture and maintain  
22  
23 74 balance.<sup>14</sup> Balance dysfunction in cerebellar disorders is most likely caused by lesions of the  
24  
25 75 medial zone of the cerebellum.<sup>15</sup> At present, the main clinical interventions to improve the  
26  
27 76 balance function in stroke rehabilitation are muscle strength training or balance training. The  
28  
29 77 activation of the cerebellar vermis in the central nervous system through neuromodulation  
30  
31 78 with noninvasive brain stimulation has great potential for enhancing balance function in  
32  
33 79 stroke patients.

34  
35  
36  
37 80 Repetitive transcranial magnetic stimulation (rTMS) is a safe, reliable, and standardized  
38  
39 81 noninvasive brain activity modulation strategy to regulate cortical excitability and facilitate  
40  
41 82 neural plasticity.<sup>16</sup> Intermittent theta-burst stimulation (iTBS) is a novel form of rTMS that  
42  
43 83 can produce long-term potentiation and is more rapid and efficacious than standard rTMS.<sup>17</sup>  
44  
45 84 Previously published studies revealed that iTBS over the cerebellar hemisphere could  
46  
47 85 promote gait and balance recovery in patients with chronic ischemic stroke.<sup>18</sup> Similarly, our  
48  
49 86 research group recently provided evidence that iTBS over the cerebellar hemisphere could  
50  
51 87 promote upper limb spasticity, balance, and walking performance recovery in poststroke  
52  
53 88 patients.<sup>19-21</sup> However, one of the results indicated that the difference in Berg Balance Scale  
54  
55 89 (BBS) scores between the cerebellar iTBS group and the sham stimulation group was 1.58  
56  
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1  
2  
3 90 points, which did not reach the minimal clinically important difference.<sup>22</sup> Therefore, the  
4  
5 91 identification of a more effective stimulation target for improving balance function after  
6  
7 92 stroke is necessary. No study has demonstrated the therapeutic effect and potential  
8  
9  
10 93 mechanism of cerebellar vermis iTBS on balance in individuals with stroke. Our preliminary  
11  
12 94 pilot study found that cerebellar vermis iTBS contributed to increasing the excitability of the  
13  
14 95 bilateral supplementary motor areas (SMAs) during balance tasks in healthy adults.<sup>23</sup>  
15  
16  
17 96

## 19 97 **Objective**

21  
22 98 Since no clinical research verifying the effectiveness of cerebellar vermis iTBS stimulation  
23  
24 99 has been reported, a randomized controlled double-blind trial will be conducted to determine  
25  
26 100 the effects of cerebellar vermis iTBS on trunk control, muscle activation and balance function  
27  
28 101 in subacute ischemic stroke patients. We hypothesize that cerebellar vermis iTBS can promote  
29  
30 102 the activation of trunk and lower limb muscles and increase the excitability of SMAs to  
31  
32 103 improve trunk control and balance function in patients with subacute ischemic stroke.  
33  
34  
35 104

## 37 105 **Methods**

### 40 106 **Study design and setting**

42  
43 107 This study will be a prospective single-centre double-blind randomized controlled clinical  
44  
45 108 trial with a 3-week intervention and 3-week follow-up. The protocol strictly follows the  
46  
47 109 Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) 2013  
48  
49 110 Statement.<sup>24</sup> Eligible participants will be randomly allocated to the experimental group or  
50  
51 111 control group in a 1:1 ratio. After routine conventional physical therapy, patients assigned to  
52  
53 112 the experimental group will receive cerebellar vermis iTBS, whereas patients assigned to the  
54  
55 113 control group will receive sham stimulation. The overall intervention period will be five days  
56  
57  
58 114 a week for three consecutive weeks. The outcomes will be measured at baseline (T0), 3 weeks  
59  
60

1  
2  
3 115 postintervention (T1), and at the 3-week follow-up (T3). The whole study will be performed  
4  
5 116 at the Department of Rehabilitation Medicine of Sichuan University West China Hospital  
6  
7 117 (Chengdu, Sichuan Province, China). Figure 1 shows the flow diagram of the study design.  
8  
9  
10 118 We plan to start subject recruitment on the 1<sup>st</sup> of December 2022 and complete the trial in  
11  
12 119 December 2025. Figure 2 illustrates the study schedule.  
13  
14  
15 120

### 17 121 **Sample size calculation**

18  
19 122 The sample size calculation was conducted via G\*power of 3.1.9.2 based on the result of the  
20  
21 123 BBS score in our published study, which indicated an estimated effect size of  $f=0.38$ .<sup>20</sup> Other  
22  
23 124 parameters were set as follows: a significance level of  $\alpha=0.05$  (two tails), power  $(1-\beta)=90\%$ ,  
24  
25 125 correlation among repeated measures=0.5, nonsphericity correction  $\epsilon=1$ , number of  
26  
27 126 measurements=3, and number of groups=2. Therefore, a sample size of  $n=40$  was obtained.  
28  
29 127 After allowing for a 15% dropout rate, a minimum total of 46 participants is needed.  
30  
31  
32  
33 128

### 35 129 **Participants**

#### 38 130 ***Recruitment***

39  
40 131 The participants will be recruited from the Department of Rehabilitation Medicine of Sichuan  
41  
42 132 University West China Hospital in Chengdu, Sichuan Province, China. After carefully  
43  
44 133 screening the inclusion and exclusion criteria, voluntary participants will be required to  
45  
46 134 provide written informed consent before the experiment.

#### 49 135 ***Inclusion criteria***

51 136 Participants will be considered for inclusion if they meet the following criteria:

52  
53  
54 137 (1) A diagnosis of ischemic stroke according to the *Diagnostic criteria of cerebrovascular*  
55  
56 138 *diseases in China (version 2019)*.<sup>25</sup>

57  
58  
59 139 (2) Aged between 18 and 65 years.  
60

- 1  
2  
3 140 (3) First-ever unilateral ischemic stroke confirmed by imaging examination.  
4  
5 141 (4) Subacute stroke participants with the stroke onset ranging from 2 weeks to 6 months.<sup>26-28</sup>  
6  
7  
8 142 (5) Having motor deficit and balance dysfunction, with a Fugl-Meyer Assessment for Lower  
9  
10 143 Extremities (FMA-LE) score <34 points and BBS score <56 points.<sup>20</sup>  
11

#### 12 144 ***Exclusion criteria***

14 145 Participants will be excluded if they meet any of the following criteria:

- 16  
17 146 (1) Diagnosis of coexisting other neurological diseases.  
18  
19 147 (2) Injury of cerebellum or brain stem.  
20  
21 148 (3) Having contraindications for iTBS (e.g., history of seizures, intracranial metallic implants,  
22  
23 149 microprocessor implants in the body, tumours, and pregnancy)  
24  
25  
26 150 (4) Cognitive impairment defined as a Mini-Mental State Examination (MMSE) score <27.  
27  
28 151 (5) Treatment with benzodiazepines, baclofen, antiepileptics and antidepressants.  
29

30 152

#### 31 153 **Interventions**

32  
33 154 All enrolled participants will receive 1 session of cerebellar vermis iTBS or sham stimulation  
34  
35 155 before routine conventional physical therapy from Monday to Friday, with a total of 15  
36  
37  
38 156 sessions. Patients in the experimental group will receive cerebellar vermis iTBS coupled with  
39  
40 157 conventional physical therapy, and those in the control group will receive sham stimulation  
41  
42 158 coupled with conventional physical therapy. The whole intervention period will last for a total  
43  
44 159 of three consecutive weeks.  
45  
46  
47  
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49 160

#### 50 161 ***Cerebellar vermis iTBS stimulation***

51  
52 162 The stimulation protocol will strictly adhere to the safety guidelines and recommendations  
53  
54 163 endorsed by the International Federation for Clinical Neurophysiology in 2021.<sup>29</sup> We will use  
55  
56 164 a Magstim Rapid2 stimulator (The Magstim Company Limited) connected to a 70 mm figure-  
57  
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1  
2  
3 165 of-8 Double Rapid2 Air Cooled Coil (P/N 3910-00) to stimulate the cerebellar vermis (Figure  
4  
5 166 3). The centre of the coil will be placed tangentially to the target scalp area, and the coil  
6  
7 167 current direction will point downwards. iTBS will be applied over the cerebellar vermis, 1 cm  
8  
9 168 inferior to the inion.<sup>30</sup> We will use a neuronavigation system (BrainSightt, Rogue Research  
10  
11 169 Inc.) coupled with a Polaris Vicra infrared camera to ensure that cerebellar vermis iTBS is  
12  
13 170 applied over the same spot for the same participant across different sessions (Figure 3). The  
14  
15 171 pattern of iTBS consists of 600 pulses containing 3 pulses at 50 Hz repeated at a rate of 5 Hz,  
16  
17 172 with 20 trains of 10 bursts given at 8 seconds intervals.<sup>31</sup> The standard stimulus intensity will  
18  
19 173 be set at 80% of the active motor threshold (AMT), which is the lowest intensity evoking at  
20  
21 174 least five out of ten motor-evoked potentials (MEPs) with a peak-to-peak amplitude >200  $\mu$ V  
22  
23 175 in the abductor pollicis brevis muscle during 10% of the maximum voluntary contraction  
24  
25 176 measured by a dynamometer.<sup>21</sup> If the participant cannot elicit MEPs or cannot tolerate the  
26  
27 177 preset standard stimulus intensity, the stimulator output intensity will be set to the  
28  
29 178 participant's maximum tolerated intensity.<sup>32</sup>  
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37

### 38 180 ***Sham stimulation***

39  
40 181 Participants in the control group will be treated identically to those in the experimental group,  
41  
42 182 except the Magstim sham coil (P/N 3950-00) will be used to deliver the sham stimulation.<sup>33</sup>  
43  
44 183 The sham coil has the same external appearance, parameters and application methods for  
45  
46 184 stimulating the sensation produced by the real coil without inducing a magnetic field.  
47  
48 185 Therefore, it can sufficiently ensure that the patients remain blinded to the intervention.  
49  
50  
51  
52

### 53 187 ***Conventional physical therapy***

54  
55 188 After receiving cerebellar vermis iTBS or sham stimulation, all participants will receive  
56  
57 189 conventional physical therapy, including limb positioning, balance exercise, trunk control,  
58  
59  
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2  
3 190 and postural and transfer training, with each session lasting 50 minutes during the intervention  
4  
5 191 phase.

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10 193 ***Criteria for discontinuing the allocated interventions***

11  
12 194 Interventions will be discontinued for participants if any of the following events occur:

13  
14 195 (1) Serious adverse events, such as epilepsy, severe headache, persistent tinnitus and syncope,

15  
16 196 occur during the stimulation.

17  
18 197 (2) Participants withdraw from the trial.

19  
20 198 (3) Participants are not compliant with the allocation and intervention plan.

21  
22 199 (4) Participants join in additional studies during the trial.

23  
24 200 (5) Group exposure for participants and outcome evaluators lead to the failure of blindness.

25  
26 201

27  
28 202 ***Improving adherence strategies***

29  
30 203 To improve the participant compliance, the researcher in charge of the trial will contact the

31  
32 204 participants regularly to clarify their rehabilitation progress and discuss the subsequent

33  
34 205 physical therapy programme. Additionally, patients who complete the entire procedure in

35  
36 206 accordance with the protocol will be provided with a subject fee and an additional free

37  
38 207 rehabilitation consultation. If a participant drops out, the specific reasons for withdrawal will

39  
40 208 be recorded.

41  
42 209

43  
44 210 **Outcome Measures**

45  
46 211 On the day of enrolment, the basic characteristics of the participants, including age, sex, type

47  
48 212 of stroke, lesion site, course of disease, degree of neurological deficit as assessed by the

49  
50 213 National Institutes of Health Stroke Scale (NIHSS), and cognitive function as assessed by the

51  
52 214 MMSE, will be documented. The outcome assessments will be conducted at the treatment site

1  
2  
3 215 at T0, T1 and T3. The primary outcomes are BBS and Trunk Impairment Scale (TIS) scores.  
4  
5 216 The secondary outcomes are balance tests via the Balance Master system, muscle activation  
6  
7 217 of the trunk and lower limbs via the surface electromyography (sEMG) recordings, cerebral  
8  
9 218 cortex oxygen concentrations measured via the resting-state functional near-infrared  
10  
11 219 spectroscopy (fNIRS), FMA-LE scores, and Barthel Index (BI) scores. Each assessment will  
12  
13 220 be performed by a professional clinician or by a qualified physical therapist who will be  
14  
15 221 blinded to the experimental condition of the participant.  
16  
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222

## 223 *Primary outcomes*

### 224 *1. BBS*

225 The BBS is a well-validated scale for assessing balance among individuals with neurological  
226 disease.<sup>34</sup> It has high reliability and internal validity, with an intraclass correlation coefficient  
227 for inter-measure reliability and intra-measure reliability of 0.97 and 0.98, respectively.<sup>35</sup> This  
228 scale is a 14-item measure with a total score of 56, and the score of each item ranges from 0  
229 (poor balance) to 4 (good balance).<sup>36</sup>

### 230 *2. TIS*

231 The TIS is a scale designed to assess motor impairment of the trunk after stroke,  
232 demonstrating the most promising performance in psychometric properties with satisfactory  
233 reliability and validity.<sup>37</sup> It is a 17-item scale used to evaluate static and dynamic sitting  
234 balance and trunk coordination for stroke patients, with a total score ranging from 0 to 23  
235 points.<sup>38</sup> A higher score indicates better trunk control.

236

## 237 *Secondary outcomes*

### 238 *1. Balance tests via the Balance Master system*

239 The assessments of dynamic balance and postural control abilities will be performed by the

240 Sensory Organization Test (SOT), Limits of Stability (LOS), and Rhythmic Weight Shift  
 241 (RWS) via the Smart Equitest Balance Master System® (NeuroCom Int., Inc., Clackamas,  
 242 Oregon, USA). (Figure 4)

243 *1.1 SOT*: The SOT evaluates postural control when participants undergo different  
 244 somatosensory, visual, and vestibular feedback perturbations. During testing, inaccurate  
 245 interference information is delivered to the patient's eyes, feet, and joints and is controlled  
 246 through calibrated sway referencing of the support surface and/or visual surroundings. The  
 247 participant is required to maintain balance to keep their centre of gravity (COG) as steady as  
 248 possible. A composite equilibrium score is provided to characterize the participant's overall  
 249 level of performance through the six conditions described in Table 1. During the SOT, each  
 250 trial lasts for 20 seconds and is repeated three times.<sup>39 40</sup>

**Table 1.** Sensory Organization Test

Condition	Vision	Surface	Surround	Interference
1	Eyes open	Stable	Fixed	Null
2	Eyes closed	Stable	Fixed	Vision
3	Eyes open	Stable	Unfixed	Vision
4	Eyes open	Unstable	Fixed	Somatosensation
5	Eyes closed	Unstable	Fixed	Somatosensation and Vision
6	Eyes open	Unstable	Unfixed	Somatosensation and Vision

251  
 252 *1.2 LOS*: The LOS quantifies the voluntary ability to shift the COG in eight different  
 253 directions: forwards, forwards-right, right, backwards-right, backwards, backwards-left, left,  
 254 and forwards-left. When the test is performed, a real-time display of the participant's COG  
 255 position in relation to targets placed at the centre of the base of support and the stability limits  
 256 is shown. Once the command is given, the participant must move their COG from a central  
 257 position out towards one of the eight targets as quickly (up to 8 seconds) and accurately as

1  
2  
3 258 possible.<sup>41</sup>  
4

5 259 *1.3 RWS*: The RWS evaluates a participant's ability to perform rhythmic movements of their  
6  
7 260 COG from left to right (lateral) and forwards to backwards (anterior/posterior) between two  
8  
9 261 targets at three different speeds (slow, medium and fast).<sup>42</sup> Movement velocity and directional  
10  
11 262 control are measured for each direction and speed.  
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13

## 14 263 **2. sEMG recordings**

15  
16 264 The sEMG recordings will be conducted in accordance with the Surface ElectroMyoGraphy  
17  
18 265 for the Non-Invasive Assessment of Muscles (SENIAM) guidelines.<sup>43</sup> A 20-channel wireless  
19  
20 266 BTS-FREEEMG 300 (BTS Biomechanics Ltd, Italy) will be used to collect the sEMG signals  
21  
22 267 of the following muscles: bilateral rectus abdominis (RA), external oblique muscle (EO),  
23  
24 268 erector spinae (longissimus), rectus femoris (RF), biceps femoris (BF), tibialis anterior (TA)  
25  
26 269 and soleus (Table 2 and Figure 5 illustrate the sensor locations on the individual muscles).  
27  
28 270 Before starting, the skin will be cleaned using 75% alcohol and would be shaved if needed to  
29  
30 271 ensure a maximum skin impedance below 5 k $\Omega$ . After skin preparation, the participant will be  
31  
32 272 put into the starting posture, depending on the muscle at which the electrodes will be placed.  
33  
34 273 A pair of pre-gelled electrodes certified for medical use and in compliance with the directive  
35  
36 274 93/42/EEC (amended by 2007/47/EC) will be placed on the belly of the target muscle with an  
37  
38 275 interelectrode distance of 2 cm.<sup>44</sup> When the electrodes are placed and fixed, a certified  
39  
40 276 physical therapist will teach the patient to perform the maximum voluntary isometric  
41  
42 277 contraction (MVIC) of the target muscle. For individual muscles, we will record three we will  
43  
44 278 record three 3 seconds MVIC trials with a 2 minutes rest period between each trial.  
45  
46 279 sEMG signals will be sampled at 1000 Hz. Collected data will be synchronously transmitted  
47  
48 280 to a BTS EMG-Analyzer (BTS Bioengineering) with the bandpass filtered from 20 to 500 Hz.  
49  
50 281 We will rectify and filter the recorded signal and extract the data of averaged  
51  
52 282 electromyography (AEMG), root mean square (RMS), mean power frequency (MPF) and  
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283 median frequency (MF) data for subsequent analyses.

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**Table 2.** The sensor locations on individual muscles for sEMG recordings \*

Muscle	Starting posture of participant	Electrode placement	
		Location	Orientation
RA	Supine or standing	2 cm superior and 2-4 cm lateral to the umbilicus	Vertical
EO	Supine or standing	At a 2-finger width above the anterior half of the iliac crest	In the direction of the line from the outside of the 5-12 ribs to the anterior half of the iliac crest
Longissimus	Prone with the lumbar vertebral columns slightly flexed	At a 2-finger width lateral from the proc. spin. of L1.	Vertical
RF	Sitting on a table with the knees in slight flexion and the upper body bend slightly backwards	At 50% on the line from the anterior spina iliaca superior to the superior part of the patella	In the direction of the line from the anterior spina iliaca superior to the superior part of the patella
BF	Lying on the belly with the face down with the thigh down on the table, the knees flexed (to less than 90 degrees), the thigh in a slight lateral rotation and the leg in a slight lateral rotation with respect to the thigh	At 50% on the line between the ischial tuberosity and the lateral epicondyle of the tibia	In the direction of the line between the ischial tuberosity and the lateral epicondyle of the tibia
TA	Supine or sitting	At 1/3 on the line between the tip of the fibula and the tip of the medial malleolus	In the direction of the line between the tip of the fibula and the tip of the medial malleolus

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Soleus	Sitting with the knee flexed approximately 90 degrees and the heel/foot of the investigated leg on the floor	At 2/3 of the line between the medial condyle of the femur to the medial malleolus	In the direction of the line between the medial condyle to the medial malleolus
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Abbreviations: sEMG, surface electromyography; RA, rectus abdominis; EO, external oblique muscle; RF, rectus femoris; BF, biceps femoris; TA, tibialis anterior.

\* According to the SENIAM recommendations for sensor locations for muscles.

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### 287 **3. Resting-state fNIRS**

288 A multichannel fNIRS system with 24 sources and 24 detectors (NirScan, HuiChuang, China)  
289 will be used to record changes in oxygenated haemoglobin (HbO<sub>2</sub>), deoxygenated Hb and  
290 total Hb of the cerebral cortex when the participant is at rest. Relevant parameters will be set  
291 as follows: the wavelengths are between 730 and 850 nm, the source-detector distance is 3  
292 cm, and the sampling frequency is over 11 Hz. The international 10/20 system is referenced  
293 for identifying optodes on the bilateral prefrontal and parietal lobes.<sup>45</sup> Collected fNIRS data  
294 will be analysed by the NirSpark software package with the bandpass filtering from 0.01 to  
295 0.1 Hz. The mean HbO<sub>2</sub> value of each channel will be extracted for statistical analyses.

### 296 **4. FMA-LE**

297 The lower extremity function of stroke patients will be assessed by FMA-LE, which has good  
298 interrater reliability and concurrent validity.<sup>46</sup> The maximum score of this 17-item scale is 34  
299 points. Each item is scored on a 3-point ordinal scale, with 0 points for inability, 1 point for  
300 partial ability, and 2 points for full ability to perform the required movement.<sup>47</sup>

### 301 **5. BI**

302 The BI is a self-reported scale comprising of 10 items, including bathing, grooming, bladder  
303 management, bowel management, dressing, feeding, toilet use, transfers, ascending and  
304 descending stairs, and walking, to measure basic activities of daily living.<sup>48</sup> The total scores  
305 vary from 0 (totally dependent) to 100 (independent). This scale has good clinimetric  
306 properties and excellent interrater reliability with standardized administration for stroke  
307 patients.<sup>19 49</sup>

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### 309 **Safety measurements**

310 Possible stimulation-related adverse events, such as headache, nausea, neck pain, seizure,  
311 mood changes, fatigue, tinnitus, dizziness, sleepiness and syncope, are listed in the informed

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2  
3 312 consent form. An adverse reaction record will be used to monitor and provide detailed reports  
4  
5 313 after each stimulation. In addition, any adverse events related to in conventional physical  
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7 314 therapy will also be recorded using the adverse event case report form (CRF).  
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## 11 316 **Randomization and blinding**

12  
13  
14 317 The study will be a randomized, double-blind, sham-controlled trial. Enrolled participants will  
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16 318 be randomly assigned based on the computer-generated random numbers that are concealed in  
17  
18 319 opaque numbered envelopes and opened in numerical order by a neutral noninvolved  
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20 320 researcher. We plan to blind the participants and evaluators. If blinding fails, the participants  
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22 321 will be removed. A sham coil will be used to ensure that the patients are blinded to the  
23  
24 322 intervention. Outcome evaluations will be conducted by a professional clinician or by a  
25  
26 323 qualified physical therapist who is blinded to the group assignment. An independent  
27  
28 324 researcher will be designated to complete the data analysis. Unblinding will be carried out  
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30 325 after the data analysis is completed. In the case of serious adverse events occurring during  
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32 326 interventions, emergency unblinding will also be implemented.  
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## 39 328 **Data management and analysis**

### 40 329 ***Data management***

41  
42 330 Data will be recorded on CRFs in a timely, complete and accurate manner. Two researchers  
43  
44 331 will independently input data into Excel software and cross-check each other. Thus, electronic  
45  
46 332 data will be stored and available to the relevant researcher only. The West China Hospital  
47  
48 333 Clinical Trials and Biomedical Ethics Committee of Sichuan University are responsible for  
49  
50 334 monitoring the safety and process of the study and have the right to terminate the trial if  
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52 335 serious advent events occur. All procedures will comply with the confidentiality standards for  
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54 336 medical data.  
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45 338 ***Statistical analysis***

7 339 Statistical analyses will be performed using GraphPad Prism 8.4.3 (GraphPad Software, Inc.,  
8 La Jolla, CA, USA) based on the intention-to-treat principle. Missing data will be imputed  
9  
10 340 using the last observation carried forwards approach. The Shapiro-Wilk test will be conducted  
11  
12 341 to evaluate the normal distribution of the data. The level of significance is set at  $\alpha = 0.05$ .  
13  
14 342 Continuous variables, ordinal variables, and categorical variables will be presented as mean  
15  
16 343 ( $\pm$ standard deviation, SD), medians (interquartile range, IQR), and number (percentage, %),  
17  
18 344 respectively. Based on different types of data, the independent-samples *t* test, Mann–Whitney  
19  
20 345 U test, and chi-square test will be used to compare demographic and baseline data between  
21  
22 346 groups. Two-way mixed measures analysis of variance with group as the between-individual  
23  
24 347 factor and time as the within-individual factor will be performed for outcome measures  
25  
26 348 analyses. Nonsphericity correction will be conducted using the Greenhouse-Geisser correction  
27  
28 349 if necessary, and Tukey's *post hoc* multiple comparison test will be applied.  
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37 352 ***Patient and public involvement***

38 353 Patients and the public will not be involved in the study design, recruitment, implementation  
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40 354 or reporting. However, the study results will be disseminated to the public through academic  
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42 355 papers and conferences.  
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49 357 **Ethical approval, trial registration and dissemination**

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51 358 The study was approved by the West China Hospital Clinical Trials and Biomedical Ethics  
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53 359 Committee of Sichuan University on May 19, 2022 (ethics reference: 2022 (573)), and will be  
54  
55 360 conducted in accordance with the Declaration of Helsinki.

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58 361 This protocol was registered on November 3rd, 2022, in the Chinese Clinical Trial Registry  
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3 362 with the registration number ChiCTR2200065369. All participants will be fully informed of  
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5 363 the study procedures and sign the informed consent form voluntarily before inclusion (see the  
6  
7 364 Appendix). The private information of all participants will be kept confidential and securely  
8  
9  
10 365 placed in a locked cabinet and will only be accessible to researchers of the study. However,  
11  
12 366 the results of this study will be published in peer-reviewed journals and disseminated at  
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14 367 academic conferences.  
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## 19 369 **Discussion**

21 370 At present, no research has revealed the effect and potential mechanism of cerebellar vermis  
22  
23 371 iTBS on balance in subacute stroke patients. This prospective single-centre double-blind  
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25 372 randomized controlled clinical trial with a 3-week intervention and 3-week follow-up is  
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27 373 designed to confirm its effectiveness.  
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31 374 Our study will comprehensively assess trunk control and balance function by clinical scales,  
32  
33 375 balance tests via the Smart Equitest Balance Master System and sEMG measurements.  
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35 376 Additionally, we will also collect the concentration of HbO<sub>2</sub> in the cerebral cortex via resting-  
36  
37 377 state fNIRS. The integrated data results will be sufficient to verify the research hypothesis.  
38

39 378 For trunk control, the TIS scores can reveal motor impairment of the trunk in stroke patients.  
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41 379 The sEMG signal directly reflects the activation of muscles directly and contains information  
42  
43 380 about movement intentions generated by the brain.<sup>50</sup> AEMG represents the degree of muscle  
44  
45 381 activation and the synchronization of activated motor units. RMS quantifies the effort of the  
46  
47 382 muscle. MPF and MF are frequency domain features and indicate muscle fatigue.<sup>51 52</sup>  
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50 383 For balance function, the BBS score reflects the overall performance of static and dynamic  
51  
52 384 balance. Accurate integration of sensory information is critical to maintaining balance. The  
53  
54 385 composite equilibrium score of the SOT characterizes the impairments of individual sensory  
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56 386 systems.<sup>53</sup> The ability to voluntarily move the COG within the LOS is fundamental to  
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3 387 mobility tasks. By the LOS test, reaction time, movement velocities and excursions are  
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5 388 recorded to measure the voluntary ability to shift the COG without losing balance. Reaction  
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7 389 time reflects the cognitive processing ability. Movement velocities indicate high-level central  
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9 390 nervous system function. Excursions can be restricted by biomechanical deficits.<sup>54</sup> Overall,  
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11 391 limitations in the LOS are associated with instability during weight-shifting activities. RWS  
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13 392 measures movement velocity and directional control during rhythmic movements. Rhythmic,  
14  
15 393 reciprocal movement patterns are required in daily activities. Stroke patients with disrupted  
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17 394 normal rhythmic movement control exhibit reduced velocities and/or poor directional control  
18  
19 395 ability.<sup>55</sup>  
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23 396 For cortical activation, fNIRS is a widespread noninvasive measurement that provides real-  
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25 397 time monitoring of haemodynamic signals to reflect changes in brain activation.<sup>56</sup> Increased  
26  
27 398 HbO<sub>2</sub> is positively correlated with cortical excitability. In addition, balance function and  
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29 399 postural stability are positively related to the changes in HbO<sub>2</sub> signals in the bilateral SMAs  
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31 400 in stroke patients.<sup>57</sup> Additionally, our previous work revealed that single-session cerebellar  
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33 401 vermis iTBS can increase bilateral SMAs excitability during balance tasks in healthy adults.<sup>23</sup>  
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35 402 We hypothesize that cerebellar vermis iTBS can promote the activation of muscles in the  
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37 403 trunk and lower limbs, and increase the excitability of the SMAs to improve trunk control and  
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39 404 balance function in patients after stroke. The cerebellar vermis plays an important role in  
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41 405 postural tone, balance, and locomotion through descending spinal pathways since the vermis  
42  
43 406 receives vestibulocerebellar and proprioceptive spinocerebellar afferents.<sup>58</sup> SMA contributes  
44  
45 407 to anticipatory postural adjustments and postural stability during gait initiation.<sup>59</sup> iTBS  
46  
47 408 consists of high-frequency stimulation bursts that strongly modulate the neural activity of the  
48  
49 409 cerebellar vermis. Studies with humans have shown that iTBS drives acute changes to motor  
50  
51 410 behaviour and neuronal excitability.<sup>60</sup> A possible mechanism has been reported by an animal  
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53 411 study showing that iTBS can promote neural structural remodelling and functional recovery  
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3 412 by enhancing neurogenesis and migration via the miR-551b-5p/BDNF/TrkB pathway.<sup>61</sup> The  
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5 413 first study of cerebellar vermis stimulation was reported in 1995, which investigated its  
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7 414 effects on saccade metrics in a man via TMS.<sup>62</sup> At present, researchers have reported that  
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9 415 cerebellar vermis stimulation is a safe and well-tolerated brain stimulation technology with a  
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11 416 potential therapeutic effect on schizophrenia.<sup>63</sup> In addition, cerebellar vermis rTMS can  
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13 417 induce a suppressive effect on pharyngeal motor cortical activity and swallowing behaviour.<sup>64</sup>  
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15 418 However, limited studies have reported that the cerebellar vermis plays an important role in  
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17 419 postural response and balance stability.<sup>13 65</sup> Therefore, we hope to identify the effectiveness of  
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19 420 cerebellar vermis iTBS in trunk control and balance function for subacute ischemic stroke  
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21 421 patients. Our results may provide valuable information for developing a novel treatment  
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23 422 method for the rehabilitation of balance dysfunction after stroke.  
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31 424 **Author contributions:** Conceptualization, validation, and original draft: YC.  
32  
33 425 Recruitment: LH, HHJ, and QCW. Data collection: YC, WS, and HXT. Data analysis: CFG  
34  
35 426 and QFG. Manuscript review and editing: CFG and QG. QG designed the trial and was  
36  
37 427 responsible for the manuscript. All authors read and approved the final manuscript.  
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55 434 **Acknowledgments:** None.  
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3 634 **Legends**  
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5 635 **Figure 1.** The flow diagram of the study design.  
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7 636 **Figure 2.** The schedule of enrolment, interventions, and assessments.  
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9 637 **Figure 3.** The Magstim Rapid2 stimulator with a BrainSight neuronavigation system.  
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11 638 **Figure 4.** The Smart Equitest Balance Master System®.  
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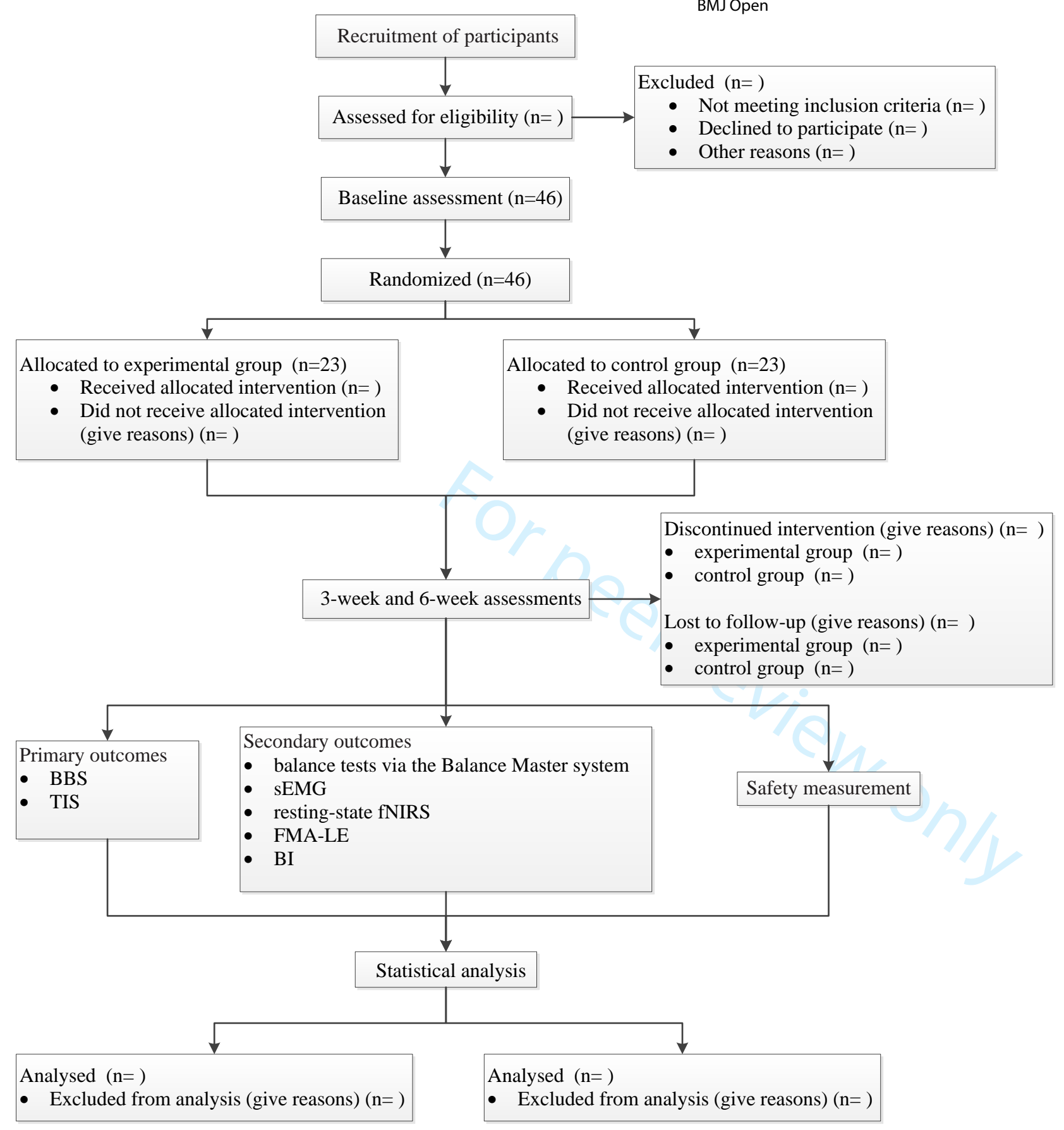
13 639 **Figure 5.** The sensor locations on individual muscles for sEMG recording (A. rectus  
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15 abdominis, B. external oblique muscle, C. rector spinae (longissimus), D. rectus femoris, E.  
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17 640 biceps femoris, F. tibialis anterior, G. soleus  
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**Enrollment**

**Intervention**

**Assessment**

**Analysis**



**Figure 2.** The schedule of enrolment, interventions, and assessments.

	Enrolment	Allocation	Post-allocation					
TIMEPOINT	$-t_1$	0	W1	W2	W3	W4	W5	W6
<b>ENROLMENT:</b>								
Eligibility screen	X							
Informed consent	X							
Ethical approval and trial registration	X							
Allocation		X						
<b>INTERVENTIONS:</b>								
cerebellar vermis iTBS and conventional physical therapy			←————→					
sham stimulation and conventional physical therapy			←————→					
<b>ASSESSMENTS:</b>								
basic characteristics information		X						
BBS		X			X			X
TIS		X			X			X
balance tests via the Balance Master system		X			X			X
sEMG		X			X			X
resting-state fNIRS		X			X			X
FMA-LE		X			X			X
BI		X			X			X
Safety measurement			X	X	X	X	X	X

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4 W, week; iTBS, intermittent theta-burst stimulation; BBS, Berg balance scale; TIS,  
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6 trunk impairment scale; sEMG, surface electromyography; fNIRS, functional near-  
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8 infrared spectroscopy; FMA-LE, Fugl-Meyer assessment scale score for lower  
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10 extremities; BI, Barthel index.  
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For peer review only



Figure 3. The Magstim Rapid2 stimulator with a BrainSight neuronavigation system.

1066x1422mm (72 x 72 DPI)



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Figure 4. The Smart Equitest Balance Master System®.  
1066x1422mm (72 x 72 DPI)



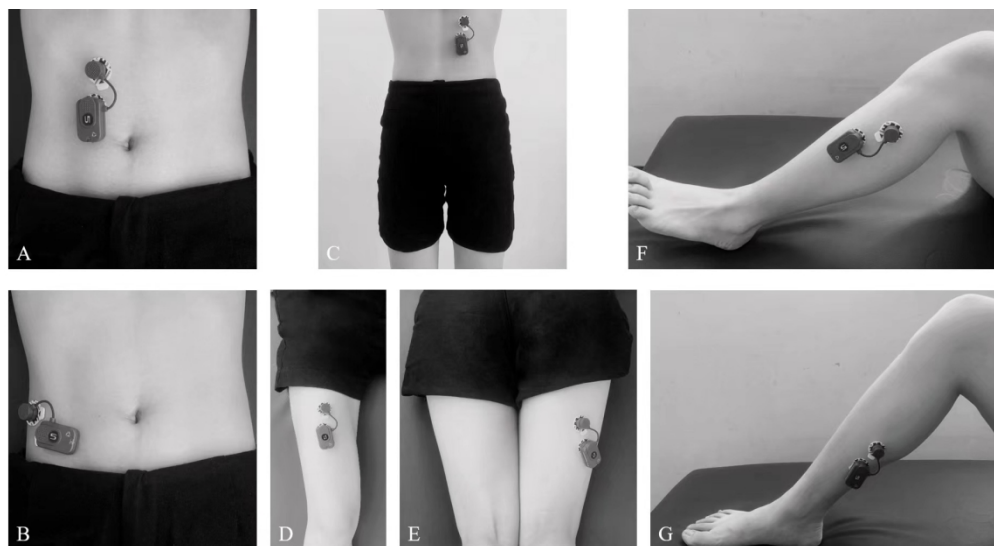


Figure 5. The sensor locations on individual muscles for sEMG recording (A. rectus abdominis, B. external oblique muscle, C. rector spinae (longissimus), D. rectus femoris, E. biceps femoris, F. tibialis anterior, G. soleus)

654x359mm (72 x 72 DPI)

## Appendix. Informed Consent Form

West China Hospital, Sichuan University			
Participant Informed Consent			
Name:	Gender:	Age:	Inpatient ID:
<p><b>Title of study:</b> The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for subacute stroke patients: a randomized controlled trial</p> <p><b>Investigator:</b> Qiang Gao</p> <p><b>Funding:</b> NSFC 82172540 from the National Natural Science Foundation of China</p> <p><b>What is the study about?</b></p> <p>(1) The aim of the study is to determine the effects of cerebellar vermis intermittent theta-burst stimulation (iTBS) on trunk control, muscle activation and balance function in stroke patients. We will recruit 46 patients who meet the inclusion criteria as follows: (1) a diagnosis of ischemic stroke according to the <i>Diagnostic criteria of cerebrovascular diseases in China (version 2019)</i>, (2) aged between 18 and 65 years, (3) first-ever unilateral ischemic stroke confirmed by imaging examination, (4) subacute stroke participants with the stroke onset ranging from 2 weeks to 6 months, (5) having motor deficit and balance dysfunction, with a Fugl-Meyer Assessment for Lower Extremities (FMA-LE) &lt;34 points and BBS score &lt;56 points. Patients were excluded if they presented one of the following: (1) diagnosis of coexisting other neurological diseases, (2) injury of cerebellar or brain stem, (3) having contraindications for iTBS (e.g., history of seizures, intracranial metallic implants, microprocessor implants in the body, tumours, and pregnancy), (4) cognitive impairment with a Mini-Mental State Examination (MMSE) score &lt;27, (5) treatment with benzodiazepines, baclofen, antiepileptics and antidepressants.</p>			

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***How long will I be in the study?***

Your part in the study will last **6 weeks** with 3 weeks of intervention and 3 weeks of follow-up (excluding assessment).

***What will happen in this study?***

You will be randomized into either the experimental or control group according to the random number table. If you assigned to the experimental group will receive cerebellar vermis iTBS after routine daily conventional physical therapy, otherwise you will receive sham stimulation after routine daily conventional physical therapy.

The overall intervention periods are five days a week for three consecutive weeks.

You will be assessed before treatment, after 3 weeks of intervention and after 3 weeks of follow-up. The measures including clinical scales, balance tests via the Balance Master system, and the surface electromyography recording.

If you are eligible and wish to join the study, you must sign this consent form. If you do not sign the consent form you cannot join the study.

We will review this consent form with you. You will be given enough time to review the consent and have all your questions about the study answered. We will give you a signed copy of the consent for your records before treatment in person.

Study staff will not know which group or study treatment you are assigned to. You should not join the study if you are not willing to take the study treatment (or join the group) you are assigned to.

***What if I have questions?***

You can contact the therapist at working hours if you have questions about the study. Qiang Gao (the director of therapists) is in charge of the study.

***Do I have to be in the study?***

You decide if you want to be in the study. Deciding not to take part will not affect your relationship with your therapist. If your therapist is an investigator for the study, you may get a second opinion from another therapist not involved in the study.

You can leave the study at any time and you do not have to give a reason. Leaving the study will not affect your relationship with your therapist.

The study investigators may ask you to leave the study if it is in your best interest.

The study investigator may ask you to leave the study if you do not follow the study rules.

***What if I don't want to be in the study?***

You can choose not to be in the study and you do not have to give a reason. You can choose to (talk to your doctor/therapist about other options, investigate outside resources on your own, etc.).

***Are there any costs?***

All study-related treatments are free.

***Will I be paid for being in the study?***

You will not be paid for being in the study.

***Are there any risks?***

There is always a small risk of a breach of confidentiality to your personal health information. However, these risks have been addressed and minimized as much as is possible.

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4 You will be told about any new information that may affect your willingness to  
5 participate in the study.  
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9 There are some possible risks and side effects as follows: headache, nausea, neck  
10 pain, seizure, mood changes, fatigue, tinnitus, dizziness, sleepiness and syncope.  
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15 If you experience any side effects while on the study contact investigator (Qiang  
16 Gao) at any time as soon as possible.  
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21 ***What if I feel I've been hurt by taking part in the study?***  
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23 If you feel you have been injured or harmed by taking part in this study, please  
24 contact investigator (Qiang Gao) at any time. If you feel you were harmed while  
25 taking part in this study, you may be treated at West China Hospital, Sichuan  
26 University. However, West China Hospital does not offer to pay the cost of this  
27 treatment.  
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32 If you feel your rights have been violated or you have harmed by this study, please  
33 contact your therapist.  
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38 ***Are there any benefits?***  
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41 It is possible you may receive some benefit from cerebellar vermis iTBS and  
42 conventional physical therapy. iTBS is a novel form of rTMS, which can produce  
43 long-term potentiation and is more rapid and efficacious than standard rTMS.  
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45 Cerebellar vermis is a cardinal structure involved in balance and motor control,  
46 which is responsible for regulating the trunk, head, neck and proximal limb muscles  
47 to control posture and maintain balance. There is no guarantee, however, that you  
48 will receive any benefit at all. Your participation will help us learn more about the  
49 effects of cerebellar vermis iTBS on trunk control, muscle activation and balance  
50 function in subacute stroke patients.  
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***Your privacy is important***

Protecting your privacy is very important to us.

During this study we will ask about your (past) and (current) medical history. This information will be used to determine your eligibility for the study and provide data for the study. Your personal health information will be kept private and only authorized study staff will have access to this information. We will use a study number instead of your name. All paper forms will be kept in a locked, secure office. All electronic data will be stored on password-protected computers. Your name will not be used in any publications or presentations about this study.

During the study, you may not be given access to medical information about you that is part of the study. When the study is over, you may request certain medical information collected about you that is part of your study medical record.

None of your personal information will be shared outside of West China Hospital.

By signing this consent form, you are stating that we can use your health information in the ways mentioned above for this study. You are not waiving any of your legal right by signing this form.

You have the right to take away your permission to use your health information collected as part of the study. In order to do this, you must send a written request to: Qiang Gao, department of rehabilitation, West China hospital, Sichuan University

Once your letter is received, no additional information about you will be collected from you for this study. Any data that were collected before we receive your letter will continue to be used for the study. Taking away your permission to use your

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4 health information will not affect your relationship with West China Hospital.  
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8 We are collecting only the personal health information that we need for the specific  
9  
10 purpose of this study. Your personal health information cannot be used for  
11  
12 additional research purpose.  
13

14  
15 The West China hospital may be required to provide copies of your personal  
16  
17 information to government agencies as required by law.  
18

19  
20  
21 Your permission to use your identifiable health information when the study is  
22  
23 complete.  
24

25 ***Signatures:***

26  
27 By signing this consent form, it means the following:

- 28  
29 ● I know my rights have not been waived by signing.  
30  
31 ● I have had all of my questions answered and I know whom to ask if I have more  
32  
33 questions.  
34  
35 ● I have read this form and understand it.  
36  
37 ● I want to join the study.  
38  
39 ● I know I can leave the study at any time and do not have to give a reason.  
40  
41  
42  
43

44 \_\_\_\_\_  
45 Signature of Participant

44 \_\_\_\_\_  
45 Date



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Page
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 17-18
	2b	All items from the World Health Organization Trial Registration Data Set	nil
Protocol version	3	Date and version identifier	nil
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, 20
	5b	Name and contact information for the trial sponsor	Title page
	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	20
	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)	nil
<b>Introduction</b>			
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	3-5
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6



## Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-6, Fig.2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6

## Methods: Assignment of interventions (for controlled trials)

Allocation:

1	Sequence	16a	Method of generating the allocation sequence (eg,	16
2	generation		computer-generated random numbers), and list of any	
3			factors for stratification. To reduce predictability of a random	
4			sequence, details of any planned restriction (eg, blocking)	
5			should be provided in a separate document that is	
6			unavailable to those who enrol participants or assign	
7			interventions	
8				
9				
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg,	16
11	concealment		central telephone; sequentially numbered, opaque, sealed	
12	mechanism		envelopes), describing any steps to conceal the sequence	
13			until interventions are assigned	
14				
15	Implementation	16c	Who will generate the allocation sequence, who will enrol	16
16			participants, and who will assign participants to interventions	
17				
18				
19	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg,	16
20			trial participants, care providers, outcome assessors, data	
21			analysts), and how	
22				
23		17b	If blinded, circumstances under which unblinding is	16
24			permissible, and procedure for revealing a participant's	
25			allocated intervention during the trial	
26				
27				
28	<b>Methods: Data collection, management, and analysis</b>			
29				
30	Data collection	18a	Plans for assessment and collection of outcome, baseline,	16
31	methods		and other trial data, including any related processes to	
32			promote data quality (eg, duplicate measurements, training	
33			of assessors) and a description of study instruments (eg,	
34			questionnaires, laboratory tests) along with their reliability	
35			and validity, if known. Reference to where data collection	
36			forms can be found, if not in the protocol	
37				
38				
39		18b	Plans to promote participant retention and complete follow-	16-17
40			up, including list of any outcome data to be collected for	
41			participants who discontinue or deviate from intervention	
42			protocols	
43				
44				
45	Data management	19	Plans for data entry, coding, security, and storage, including	16
46			any related processes to promote data quality (eg, double	
47			data entry; range checks for data values). Reference to	
48			where details of data management procedures can be	
49			found, if not in the protocol	
50				
51				
52	Statistical methods	20a	Statistical methods for analysing primary and secondary	17
53			outcomes. Reference to where other details of the statistical	
54			analysis plan can be found, if not in the protocol	
55				
56		20b	Methods for any additional analyses (eg, subgroup and	17
57			adjusted analyses)	
58				
59				
60				

1	20c	Definition of analysis population relating to protocol non-	17
2		adherence (eg, as randomised analysis), and any statistical	
3		methods to handle missing data (eg, multiple imputation)	
4			
5	<b>Methods: Monitoring</b>		
6			
7	Data monitoring	21a	Composition of data monitoring committee (DMC); summary
8			of its role and reporting structure; statement of whether it is
9			independent from the sponsor and competing interests; and
10			reference to where further details about its charter can be
11			found, if not in the protocol. Alternatively, an explanation of
12			why a DMC is not needed
13			
14			
15		21b	Description of any interim analyses and stopping guidelines,
16			including who will have access to these interim results and
17			make the final decision to terminate the trial
18			
19	Harms	22	Plans for collecting, assessing, reporting, and managing
20			solicited and spontaneously reported adverse events and
21			other unintended effects of trial interventions or trial conduct
22			
23			
24	Auditing	23	Frequency and procedures for auditing trial conduct, if any,
25			and whether the process will be independent from
26			investigators and the sponsor
27			
28			
29	<b>Ethics and dissemination</b>		
30			
31	Research ethics	24	Plans for seeking research ethics committee/institutional
32	approval		review board (REC/IRB) approval
33			
34	Protocol	25	Plans for communicating important protocol modifications
35	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to
36			relevant parties (eg, investigators, REC/IRBs, trial
37			participants, trial registries, journals, regulators)
38			
39			
40	Consent or assent	26a	Who will obtain informed consent or assent from potential
41			trial participants or authorised surrogates, and how (see
42			Item 32)
43			
44		26b	Additional consent provisions for collection and use of
45			participant data and biological specimens in ancillary
46			studies, if applicable
47			
48			
49	Confidentiality	27	How personal information about potential and enrolled
50			participants will be collected, shared, and maintained in
51			order to protect confidentiality before, during, and after the
52			trial
53			
54	Declaration of	28	Financial and other competing interests for principal
55	interests		investigators for the overall trial and each study site
56			
57			
58	Access to data	29	Statement of who will have access to the final trial dataset,
59			and disclosure of contractual agreements that limit such
60			access for investigators

1	Ancillary and post-	30	Provisions, if any, for ancillary and post-trial care, and for	nil
2	trial care		compensation to those who suffer harm from trial	
3			participation	
4				
5	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial	17-18
6			results to participants, healthcare professionals, the public,	
7			and other relevant groups (eg, via publication, reporting in	
8			results databases, or other data sharing arrangements),	
9			including any publication restrictions	
10				
11				
12		31b	Authorship eligibility guidelines and any intended use of	nil
13			professional writers	
14				
15		31c	Plans, if any, for granting public access to the full protocol,	nil
16			participant-level dataset, and statistical code	
17				
18				
19	<b>Appendices</b>			
20				
21	Informed consent	32	Model consent form and other related documentation given	Supplementary
22	materials		to participants and authorised surrogates	material
23				
24	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of	not applicable
25			biological specimens for genetic or molecular analysis in the	
26			current trial and for future use in ancillary studies, if	
27			applicable	
28				

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for patients with subacute stroke: a randomized controlled trial protocol

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Date Submitted by the Author:	23-Dec-2022
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<b>Primary Subject Heading</b>:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	Stroke < NEUROLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Motor neurone disease < NEUROLOGY

SCHOLARONE™  
Manuscripts

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4 1 **The effectiveness of cerebellar vermis intermittent theta burst**  
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7 2 **stimulation in improving trunk control and balance function for**  
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10 3 **patients with subacute stroke: a randomized controlled trial**  
11  
12  
13 4 **protocol**  
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18  
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45 15 **Word count:** 3999 words  
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3 17  
4 18 **Abstract**

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6  
7 19 **Introduction** Balance impairments frequently occur after stroke. Achieving effective core  
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9 20 trunk stability is the key to improving balance ability. However, there is still a lack of  
10  
11 21 advanced well-defined rehabilitation protocols for balance improvement in patients with  
12  
13 22 stroke. Intermittent theta-burst stimulation (iTBS) is a noninvasive brain activity modulation  
14  
15 23 strategy that can produce long-term potentiation. The cerebellar vermis is a fundamental  
16  
17 24 structure involved in balance and motor control. However, no study has demonstrated the  
18  
19 25 therapeutic effect and potential mechanism of cerebellar vermis iTBS on balance after stroke.  
20  
21

22  
23 26 **Methods and Analysis** This study will be a prospective single-centre double-blind  
24  
25 27 randomized controlled clinical trial with a 3-week intervention and 3-week follow-up.  
26  
27 28 Eligible participants will be randomly allocated to the experimental group or the control  
28  
29 29 group in a 1:1 ratio. After routine conventional physical therapy, patients in the experimental  
30  
31 30 group will receive cerebellar vermis iTBS, whereas patients in the control group will receive  
32  
33 31 sham stimulation. The overall intervention period will be five days a week for three  
34  
35 32 consecutive weeks. The outcomes will be measured at baseline (T0), 3 weeks postintervention  
36  
37 33 (T1) and at the 3-week follow-up (T2). The primary outcomes are Berg Balance Scale (BBS)  
38  
39 34 and Trunk Impairment Scale (TIS) scores. The secondary outcomes are balance tests scores  
40  
41 35 via the Balance Master system, muscle activation of the trunk and lower limbs via the surface  
42  
43 36 electromyography (sEMG) recordings, cerebral cortex oxygen concentrations measured via  
44  
45 37 the resting-state functional near-infrared spectroscopy (fNIRS), and Fugl-Meyer Assessment  
46  
47 38 of Lower Extremity (FMA-LE) and Barthel index (BI) scores.  
48  
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50

51 39 **Ethics and Dissemination** This study was approved by the West China Hospital Clinical  
52  
53 40 Trials and Biomedical Ethics Committee of Sichuan University. The trial registration number  
54  
55 41 is ChiCTR2200065369. All participants will sign the informed consent form voluntarily. The  
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3 42 results of this study will be published in peer-reviewed journals and disseminated at academic  
4  
5 43 conferences.  
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8 44

## 10 45 **Strengths and limitations of this study**

- 13 46 ➤ Our study comprehensively assesses the trunk control and balance function by clinical  
14  
15 47 scales, balance tests via the Smart Equitest Balance Master System, and surface  
16  
17 48 electromyography (sEMG) measurements.
- 20 49 ➤ Resting-state functional near-infrared spectroscopy (fNIRS) will be used to collect the  
21  
22 50 concentration of HbO<sub>2</sub> in the cerebral cortex.
- 24 51 ➤ This study lacks a long-term follow-up assessment.  
25  
26  
27 52

## 30 53 **Introduction**

32 54 Stroke is the third most common cause of disability worldwide.<sup>1</sup> The incidents, prevalence,  
33  
34 55 and disability-adjusted life-years of stroke have increased over the past two decades<sup>2</sup>, and are  
35  
36 56 considered to place heavy economic burdens on society. Balance impairments frequently  
37  
38 57 occur in patients with stroke, with a reported incidence ranging from 61% to 83%<sup>3</sup>. The main  
39  
40 58 manifestations are postural instability, weak trunk control, and difficulty shifting weight,<sup>4</sup>  
41  
42 59 which ultimately result in falls, poor mobility, decreased physical activity, and reduced  
43  
44 60 quality of life in patients.<sup>5</sup> Therefore, improvement of balance function is a cardinal  
45  
46 61 requirement in patients with stroke.

50 62 The trunk plays a fundamental role in trunk control, balance, and mobility during sitting and  
51  
52 63 transferring.<sup>6</sup> The synchronized activity of trunk muscles is necessary for maintaining  
53  
54 64 dynamic balance. In addition, proper trunk muscle control is essential for stabilizing distal  
55  
56 65 limbs.<sup>7</sup> Muscle weakness of the lower limbs is associated with decreased standing balance  
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2  
3 66 control.<sup>8</sup> Impaired trunk control and core muscle weakness attenuate balance and physical  
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5 67 function in individuals after stroke.<sup>9</sup> Therefore, achieving effective core trunk stability is  
6  
7 68 crucial to improving balance ability after stroke.

8  
9  
10 69 The cerebellum, a central brain structure located in the posterior cranial fossa, works in  
11  
12 70 concert with the cerebral cortex, brainstem, and spinal cord and is involved in motor control.<sup>10</sup>

13  
14 71 <sup>11</sup> It consists of two lateral hemispheres and the cerebellar vermis. The cerebellar vermis is a  
15  
16 72 fundamental structure involved in balance and motor processing,<sup>12 13</sup> and is responsible for  
17  
18 73 regulating the trunk, head, neck and proximal limb muscles to control posture and maintain  
19  
20 74 balance.<sup>14</sup> Balance dysfunction in cerebellar disorders is most likely caused by lesions of the  
21  
22 75 medial zone of the cerebellum.<sup>15</sup> At present, the main clinical interventions to improve the  
23  
24 76 balance function in stroke rehabilitation are muscle strength training or balance training. The  
25  
26 77 activation of the cerebellar vermis in the central nervous system through neuromodulation  
27  
28 78 with noninvasive brain stimulation has great potential for enhancing balance function in  
29  
30 79 patients with stroke.

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32  
33 80 Repetitive transcranial magnetic stimulation (rTMS) is a safe, reliable, and standardized  
34  
35 81 noninvasive brain activity modulation strategy to regulate cortical excitability and facilitate  
36  
37 82 neural plasticity.<sup>16</sup> Intermittent theta-burst stimulation (iTBS) is a novel form of rTMS that  
38  
39 83 can produce long-term potentiation and is more rapid and efficacious than standard rTMS.<sup>17</sup>  
40  
41 84 Previously published studies revealed that iTBS over the cerebellar hemisphere could  
42  
43 85 promote gait and balance recovery in patients with chronic ischemic stroke.<sup>18</sup> Similarly, our  
44  
45 86 research group recently provided evidence that iTBS over the cerebellar hemisphere could  
46  
47 87 promote upper limb spasticity, balance, and walking performance recovery in patients with  
48  
49 88 stroke.<sup>19-21</sup> However, one of the results indicated that the difference in Berg Balance Scale  
50  
51 89 (BBS) scores between the cerebellar iTBS group and the sham stimulation group was 1.58  
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53 90 points, which did not reach the minimal clinically important difference.<sup>22</sup> Therefore, the  
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3 91 identification of a more effective stimulation target for improving balance function after  
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5 92 stroke is necessary. No study has demonstrated the therapeutic effect and potential  
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7 93 mechanism of cerebellar vermis iTBS on balance in individuals with stroke. Our preliminary  
8  
9 94 pilot study found that cerebellar vermis iTBS contributed to increasing the excitability of the  
10  
11 95 bilateral supplementary motor areas (SMAs) during balance tasks in healthy adults.<sup>23</sup>  
12  
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15 96

## 17 97 **Objective**

18  
19 98 Since no clinical research verifying the effectiveness of cerebellar vermis iTBS stimulation  
20  
21 99 has been reported, a randomized controlled double-blind trial will be conducted to determine  
22  
23 100 the effects of cerebellar vermis iTBS on trunk control, muscle activation and balance function  
24  
25 101 in patients with subacute ischemic stroke. We hypothesize that cerebellar vermis iTBS can  
26  
27 102 promote the activation of trunk and lower limb muscles and increase the excitability of SMAs  
28  
29 103 to improve trunk control and balance function in patients with subacute ischemic stroke.  
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31 104

## 35 105 **Methods**

### 38 106 **Study design and setting**

39  
40 107 This study will be a prospective single-centre double-blind randomized controlled clinical  
41  
42 108 trial with a 3-week intervention and 3-week follow-up. The protocol strictly follows the  
43  
44 109 Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) 2013  
45  
46 110 Statement.<sup>24</sup> Eligible participants will be randomly allocated to the experimental group or  
47  
48 111 control group in a 1:1 ratio. After routine conventional physical therapy, patients assigned to  
49  
50 112 the experimental group will receive cerebellar vermis iTBS, whereas patients assigned to the  
51  
52 113 control group will receive sham stimulation. The overall intervention period will be five days  
53  
54 114 a week for three consecutive weeks. The outcomes will be measured at baseline (T0), 3 weeks  
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56 115 postintervention (T1), and at the 3-week follow-up (T2). The whole study will be performed  
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2  
3 116 at the Department of Rehabilitation Medicine of Sichuan University West China Hospital  
4  
5 117 (Chengdu, Sichuan Province, China). Figure 1 shows the flow diagram of the study design.  
6  
7 118 We plan to start subject recruitment on the 1<sup>st</sup> of December 2022 and complete the trial in  
8  
9  
10 119 December 2025. Figure 2 illustrates the study schedule.  
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12  
13  
14

### 15 121 **Sample size calculation**

16  
17 122 The sample size calculation was conducted via G\*power of 3.1.9.2 based on the result of the  
18  
19 123 BBS score in our published study, which indicated an estimated effect size of  $f=0.38$ .<sup>20</sup> Other  
20  
21 124 parameters were set as follows: a significance level of  $\alpha=0.05$  (two tails), power  $(1-\beta)=90\%$ ,  
22  
23 125 correlation among repeated measures=0.5, nonsphericity correction  $\epsilon=1$ , number of  
24  
25 126 measurements=3, and number of groups=2. Therefore, a sample size of  $n=40$  was obtained.  
26  
27 127 After allowing for a 15% dropout rate, a minimum total of 46 participants is needed.  
28  
29  
30

### 31 128 32 33 129 **Participants**

#### 34 130 ***Recruitment***

35  
36 131 The participants will be recruited from the Department of Rehabilitation Medicine of Sichuan  
37  
38 132 University West China Hospital in Chengdu, Sichuan Province, China. After carefully  
39  
40 133 screening the inclusion and exclusion criteria, voluntary participants will be required to  
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42 134 provide written informed consent before the experiment.  
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#### 46 135 ***Inclusion criteria***

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48 136 Participants will be considered for inclusion if they meet the following criteria:

- 49  
50 137 (1) A diagnosis of ischemic stroke according to the *Diagnostic criteria of cerebrovascular*  
51  
52 138 *diseases in China (version 2019)*.<sup>25</sup>  
53  
54 139 (2) Aged between 18 and 65 years.  
55  
56 140 (3) First-ever unilateral ischemic stroke confirmed by imaging examination.  
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3 141 (4) Participants with subacute stroke, the stroke onset ranging from 2 weeks to 6 months.<sup>26-28</sup>

4  
5 142 (5) Having motor deficit and balance dysfunction, with a Fugl-Meyer Assessment for Lower

6  
7 143 Extremities (FMA-LE) score <34 points and BBS score <56 points.<sup>20</sup>

8  
9  
10 144 ***Exclusion criteria***

11  
12 145 Participants will be excluded if they meet any of the following criteria:

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14 146 (1) Diagnosis of coexisting other neurological diseases.

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16 147 (2) Injury of cerebellum or brain stem.

17  
18 148 (3) Having contraindications for iTBS (e.g., history of seizures, intracranial metallic implants,

19  
20 149 microprocessor implants in the body, tumours, and pregnancy)

21  
22 150 (4) Cognitive impairment defined as a Mini-Mental State Examination (MMSE) score <27.

23  
24 151 (5) Treatment with benzodiazepines, baclofen, antiepileptics and antidepressants.

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26 152

27  
28 153 **Interventions**

29  
30 154 All enrolled participants will receive 1 session of cerebellar vermis iTBS or sham stimulation

31  
32 155 before routine conventional physical therapy from Monday to Friday, with a total of 15

33  
34 156 sessions. Patients in the experimental group will receive cerebellar vermis iTBS coupled with

35  
36 157 conventional physical therapy, and those in the control group will receive sham stimulation

37  
38 158 coupled with conventional physical therapy. The whole intervention period will last for a total

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40 159 of three consecutive weeks.

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43  
44 161 ***Cerebellar vermis iTBS stimulation***

45  
46 162 The stimulation protocol will strictly adhere to the safety guidelines and recommendations

47  
48 163 endorsed by the International Federation for Clinical Neurophysiology in 2021.<sup>29</sup> We will use

49  
50 164 a Magstim Rapid2 stimulator (The Magstim Company Limited) connected to a 70 mm figure-

51  
52 165 of-8 Double Rapid2 Air Cooled Coil (P/N 3910-00) to stimulate the cerebellar vermis (Figure

1  
2  
3 166 3). The centre of the coil will be placed tangentially to the target scalp area, and the coil  
4  
5 167 current direction will point downwards. iTBS will be applied over the cerebellar vermis, 1 cm  
6  
7 168 inferior to theinion.<sup>30</sup> We will use a neuronavigation system (BrainSightt, Rogue Research  
8  
9 169 Inc.) coupled with a Polaris Vicra infrared camera to ensure that cerebellar vermis iTBS is  
10  
11 170 applied over the same spot for the same participant across different sessions (Figure 3). The  
12  
13 171 pattern of iTBS consists of 600 pulses containing 3 pulses at 50 Hz repeated at a rate of 5 Hz,  
14  
15 172 with 20 trains of 10 bursts given at 8 seconds intervals.<sup>31</sup> The standard stimulus intensity will  
16  
17 173 be set at 80% of the active motor threshold (AMT), which is the lowest intensity evoking at  
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19 174 least five out of ten motor-evoked potentials (MEPs) with a peak-to-peak amplitude >200  $\mu$ V  
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22  
23 175 in the abductor pollicis brevis muscle during 10% of the maximum voluntary contraction  
24  
25 176 measured by a dynamometer.<sup>21</sup> If the participant cannot elicit MEPs or cannot tolerate the  
26  
27 177 preset standard stimulus intensity, the stimulator output intensity will be set to the  
28  
29  
30 178 participant's maximum tolerated intensity.<sup>32</sup>  
31  
32

179

### 180 ***Sham stimulation***

181 Participants in the control group will be treated identically to those in the experimental group,  
182 except the Magstim sham coil (P/N 3950-00) will be used to deliver the sham stimulation.<sup>33</sup>  
183 The sham coil has the same external appearance, parameters and application methods for  
184 stimulating the sensation produced by the real coil without inducing a magnetic field.  
185 Therefore, it can sufficiently ensure that the patients remain blinded to the intervention.

186

### 187 ***Conventional physical therapy***

188 After receiving cerebellar vermis iTBS or sham stimulation, all participants will receive  
189 conventional physical therapy, including limb positioning, balance exercise, trunk control,  
190 and postural and transfer training, with each session lasting 50 minutes during the intervention

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3 191 phase.

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7  
8 193 ***Criteria for discontinuing the allocated interventions***

9  
10 194 Interventions will be discontinued for participants if any of the following events occur:

11  
12 195 (1) Serious adverse events, such as epilepsy, severe headache, persistent tinnitus and syncope,  
13  
14 196 occur during the stimulation.

15  
16  
17 197 (2) Participants withdraw from the trial.

18  
19 198 (3) Participants are not compliant with the allocation and intervention plan.

20  
21 199 (4) Participants join in additional studies during the trial.

22  
23 200 (5) Group exposure for participants and outcome evaluators lead to the failure of blindness.

24  
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27  
28 202 ***Improving adherence strategies***

29  
30 203 To improve the participant compliance, the researcher in charge of the trial will contact the

31  
32 204 participants regularly to clarify their rehabilitation progress and discuss the subsequent

33  
34 205 physical therapy programme. Additionally, patients who complete the entire procedure in

35  
36 206 accordance with the protocol will be provided with a subject fee and an additional free

37  
38 207 rehabilitation consultation. If a participant drops out, the specific reasons for withdrawal will

39  
40 208 be recorded.

41  
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45  
46 210 **Outcome Measures**

47  
48 211 On the day of enrolment, the basic characteristics of the participants, including age, sex, type

49  
50 212 of stroke, lesion site, course of disease, degree of neurological deficit as assessed by the

51  
52 213 National Institutes of Health Stroke Scale (NIHSS), and cognitive function as assessed by the

53  
54 214 MMSE, will be documented. The outcome assessments will be conducted at the treatment site

55  
56 215 at T0, T1 and T2. The primary outcomes are BBS and Trunk Impairment Scale (TIS) scores.

1  
2  
3 216 The secondary outcomes are balance tests via the Balance Master system, muscle activation  
4  
5 217 of the trunk and lower limbs via the surface electromyography (sEMG) recordings, cerebral  
6  
7 218 cortex oxygen concentrations measured via the resting-state functional near-infrared  
8  
9  
10 219 spectroscopy (fNIRS), FMA-LE scores, and Barthel Index (BI) scores. Each assessment will  
11  
12 220 be performed by a professional clinician or by a qualified physical therapist who will be  
13  
14 221 blinded to the experimental condition of the participant.  
15  
16  
17 222

## 18 19 223 *Primary outcomes*

### 20 21 224 *1. BBS*

22  
23 225 The BBS is a well-validated scale for assessing balance among individuals with neurological  
24  
25 226 disease.<sup>34</sup> It has high reliability and internal validity, with an intraclass correlation coefficient  
26  
27 227 for inter-measure reliability and intra-measure reliability of 0.97 and 0.98, respectively.<sup>35</sup> This  
28  
29 228 scale is a 14-item measure with a total score of 56, and the score of each item ranges from 0  
30  
31 229 (poor balance) to 4 (good balance).<sup>36</sup>

### 32 33 230 *2. TIS*

34  
35 231 The TIS is a scale designed to assess motor impairment of the trunk after stroke,  
36  
37 232 demonstrating the most promising performance in psychometric properties with satisfactory  
38  
39 233 reliability and validity.<sup>37</sup> It is a 17-item scale used to evaluate static and dynamic sitting  
40  
41 234 balance and trunk coordination for patients with stroke, with a total score ranging from 0 to  
42  
43 235 23 points.<sup>38</sup> A higher score indicates better trunk control.  
44  
45  
46  
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48  
49 236

## 50 51 237 *Secondary outcomes*

### 52 53 238 *1. Balance tests via the Balance Master system*

54  
55 239 The assessments of dynamic balance and postural control abilities will be performed by the  
56  
57 240 Sensory Organization Test (SOT), Limits of Stability (LOS), and Rhythmic Weight Shift  
58  
59  
60

241 (RWS) via the Smart Equitest Balance Master System® (NeuroCom Int., Inc., Clackamas,  
242 Oregon, USA). (Figure 4)

243 *1.1 SOT*: The SOT evaluates postural control when participants undergo different  
244 somatosensory, visual, and vestibular feedback perturbations. During testing, inaccurate  
245 interference information is delivered to the patient's eyes, feet, and joints and is controlled  
246 through calibrated sway referencing of the support surface and/or visual surroundings. The  
247 participant is required to maintain balance to keep their centre of gravity (COG) as steady as  
248 possible. A composite equilibrium score is provided to characterize the participant's overall  
249 level of performance through the six conditions described in Table 1. During the SOT, each  
250 trial lasts for 20 seconds and is repeated three times.<sup>39 40</sup>

**Table 1.** Sensory Organization Test

Condition	Vision	Surface	Surround	Interference
1	Eyes open	Stable	Fixed	Null
2	Eyes closed	Stable	Fixed	Vision
3	Eyes open	Stable	Unfixed	Vision
4	Eyes open	Unstable	Fixed	Somatosensation
5	Eyes closed	Unstable	Fixed	Somatosensation and Vision
6	Eyes open	Unstable	Unfixed	Somatosensation and Vision

251  
252 *1.2 LOS*: The LOS quantifies the voluntary ability to shift the COG in eight different  
253 directions: forwards, forwards-right, right, backwards-right, backwards, backwards-left, left,  
254 and forwards-left. When the test is performed, a real-time display of the participant's COG  
255 position in relation to targets placed at the centre of the base of support and the stability limits  
256 is shown. Once the command is given, the participant must move their COG from a central  
257 position out towards one of the eight targets as quickly (up to 8 seconds) and accurately as  
258 possible.<sup>41</sup>



1  
2  
3 259 1.3 RWS: The RWS evaluates a participant's ability to perform rhythmic movements of their  
4  
5 260 COG from left to right (lateral) and forwards to backwards (anterior/posterior) between two  
6  
7 261 targets at three different speeds (slow, medium and fast).<sup>42</sup> Movement velocity and directional  
8  
9 262 control are measured for each direction and speed.

## 12 263 2. sEMG recordings

14 264 The sEMG recordings will be conducted in accordance with the Surface ElectroMyoGraphy  
15  
16 265 for the Non-Invasive Assessment of Muscles (SENIAM) guidelines.<sup>43</sup> A 20-channel wireless  
17  
18 266 BTS-FREEEMG 300 (BTS Biomechanics Ltd, Italy) will be used to collect the sEMG signals  
19  
20 267 of the following muscles: bilateral rectus abdominis (RA), external oblique muscle (EO),  
21  
22 268 erector spinae (longissimus), rectus femoris (RF), biceps femoris (BF), tibialis anterior (TA)  
23  
24 269 and soleus (Table 2 and Figure 5 illustrate the sensor locations on the individual muscles).

25  
26 270 Before starting, the skin will be cleaned using 75% alcohol and would be shaved if needed to  
27  
28 271 ensure a maximum skin impedance below 5 k $\Omega$ . After skin preparation, the participant will be  
29  
30 272 put into the starting posture, depending on the muscle at which the electrodes will be placed.

31  
32 273 A pair of pre-gelled electrodes certified for medical use and in compliance with the directive  
33  
34 274 93/42/EEC (amended by 2007/47/EC) will be placed on the belly of the target muscle with an  
35  
36 275 interelectrode distance of 2 cm.<sup>44</sup> When the electrodes are placed and fixed, a certified  
37  
38 276 physical therapist will teach the patient to perform the maximum voluntary isometric  
39  
40 277 contraction (MVIC) of the target muscle. For individual muscles, we will record three we will  
41  
42 278 record three 3 seconds MVIC trials with a 2 minutes rest period between each trial.

43  
44 279 sEMG signals will be sampled at 1000 Hz. Collected data will be synchronously transmitted  
45  
46 280 to a BTS EMG-Analyzer (BTS Bioengineering) with the bandpass filtered from 20 to 500 Hz.  
47  
48 281 We will rectify and filter the recorded signal and extract the data of averaged  
49  
50 282 electromyography (AEMG), root mean square (RMS), mean power frequency (MPF) and  
51  
52 283 median frequency (MF) data for subsequent analyses.  
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**Table 2.** The sensor locations on individual muscles for sEMG recordings \*

Muscle	Starting posture of participant	Electrode placement	
		Location	Orientation
RA	Supine or standing	2 cm superior and 2-4 cm lateral to the umbilicus	Vertical
EO	Supine or standing	At a 2-finger width above the anterior half of the iliac crest	In the direction of the line from the outside of the 5-12 ribs to the anterior half of the iliac crest
Longissimus	Prone with the lumbar vertebral columns slightly flexed	At a 2-finger width lateral from the proc. spin. of L1.	Vertical
RF	Sitting on a table with the knees in slight flexion and the upper body bend slightly backwards	At 50% on the line from the anterior spina iliaca superior to the superior part of the patella	In the direction of the line from the anterior spina iliaca superior to the superior part of the patella
BF	Lying on the belly with the face down with the thigh down on the table, the knees flexed (to less than 90 degrees), the thigh in a slight lateral rotation and the leg in a slight lateral rotation with respect to the thigh	At 50% on the line between the ischial tuberosity and the lateral epicondyle of the tibia	In the direction of the line between the ischial tuberosity and the lateral epicondyle of the tibia
TA	Supine or sitting	At 1/3 on the line between the tip of the fibula and the tip of the medial malleolus	In the direction of the line between the tip of the fibula and the tip of the medial malleolus

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Soleus	Sitting with the knee flexed approximately 90 degrees and the heel/foot of the investigated leg on the floor	At 2/3 of the line between the medial condyle of the femur to the medial malleolus	In the direction of the line between the medial condyle to the medial malleolus
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Abbreviations: sEMG, surface electromyography; RA, rectus abdominis; EO, external oblique muscle; RF, rectus femoris; BF, biceps femoris; TA, tibialis anterior.

\* According to the SENIAM recommendations for sensor locations for muscles.

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### 287 **3. Resting-state fNIRS**

288 A multichannel fNIRS system with 24 sources and 24 detectors (NirScan, HuiChuang, China)  
289 will be used to record changes in oxygenated haemoglobin (HbO<sub>2</sub>), deoxygenated Hb and  
290 total Hb of the cerebral cortex when the participant is at rest. Relevant parameters will be set  
291 as follows: the wavelengths are between 730 and 850 nm, the source-detector distance is 3  
292 cm, and the sampling frequency is over 11 Hz. The international 10/20 system is referenced  
293 for identifying optodes on the bilateral prefrontal and parietal lobes.<sup>45</sup> Collected fNIRS data  
294 will be analysed by the NirSpark software package with the bandpass filtering from 0.01 to  
295 0.1 Hz. The mean HbO<sub>2</sub> value of each channel will be extracted for statistical analyses.

### 296 **4. FMA-LE**

297 The lower extremity function of patients with stroke will be assessed by FMA-LE, which has  
298 good interrater reliability and concurrent validity.<sup>46</sup> The maximum score of this 17-item scale  
299 is 34 points. Each item is scored on a 3-point ordinal scale, with 0 points for inability, 1 point  
300 for partial ability, and 2 points for full ability to perform the required movement.<sup>47</sup>

### 301 **5. BI**

302 The BI is a self-reported scale comprising of 10 items, including bathing, grooming, bladder  
303 management, bowel management, dressing, feeding, toilet use, transfers, ascending and  
304 descending stairs, and walking, to measure basic activities of daily living.<sup>48</sup> The total scores  
305 vary from 0 (totally dependent) to 100 (independent). This scale has good clinimetric  
306 properties and excellent interrater reliability with standardized administration for patients with  
307 stroke.<sup>19 49</sup>

308

### 309 **Safety measurements**

310 Possible stimulation-related adverse events, such as headache, nausea, neck pain, seizure,  
311 mood changes, fatigue, tinnitus, dizziness, sleepiness and syncope, are listed in the informed

1  
2  
3 312 consent form. An adverse reaction record will be used to monitor and provide detailed reports  
4  
5 313 after each stimulation. In addition, any adverse events related to in conventional physical  
6  
7 314 therapy will also be recorded using the adverse event case report form (CRF).  
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## 11 316 **Randomization and blinding**

12  
13  
14 317 The study will be a randomized, double-blind, sham-controlled trial. Enrolled participants will  
15  
16 318 be randomly assigned based on the computer-generated random numbers that are concealed in  
17  
18 319 opaque numbered envelopes and opened in numerical order by a neutral noninvolved  
19  
20 320 researcher. We plan to blind the participants and evaluators. If blinding fails, the participants  
21  
22 321 will be removed. A sham coil will be used to ensure that the patients are blinded to the  
23  
24 322 intervention. Outcome evaluations will be conducted by a professional clinician or by a  
25  
26 323 qualified physical therapist who is blinded to the group assignment. An independent  
27  
28 324 researcher will be designated to complete the data analysis. Unblinding will be carried out  
29  
30 325 after the data analysis is completed. In the case of serious adverse events occurring during  
31  
32 326 interventions, emergency unblinding will also be implemented.  
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38 327

## 39 328 **Data management and analysis**

### 40 329 ***Data management***

41  
42 330 Data will be recorded on CRFs in a timely, complete and accurate manner. Two researchers  
43  
44 331 will independently input data into Excel software and cross-check each other. Thus, electronic  
45  
46 332 data will be stored and available to the relevant researcher only. The West China Hospital  
47  
48 333 Clinical Trials and Biomedical Ethics Committee of Sichuan University are responsible for  
49  
50 334 monitoring the safety and process of the study and have the right to terminate the trial if  
51  
52 335 serious advent events occur. All procedures will comply with the confidentiality standards for  
53  
54 336 medical data.  
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3 337  
45 338 ***Statistical analysis***

6  
7 339 Statistical analyses will be performed using GraphPad Prism 8.4.3 (GraphPad Software, Inc.,  
8  
9  
10 340 La Jolla, CA, USA) based on the intention-to-treat principle. Missing data will be imputed  
11  
12 341 using the last observation carried forwards approach. The Shapiro-Wilk test will be conducted  
13  
14 342 to evaluate the normal distribution of the data. The level of significance is set at  $\alpha = 0.05$ .  
15  
16 343 Continuous variables, ordinal variables, and categorical variables will be presented as mean  
17  
18 344 ( $\pm$ standard deviation, SD), medians (interquartile range, IQR), and number (percentage, %),  
19  
20 345 respectively. Based on different types of data, the independent-samples *t* test, Mann–Whitney  
21  
22 346 U test, and chi-square test will be used to compare demographic and baseline data between  
23  
24 347 groups. Two-way mixed measures analysis of variance with group as the between-individual  
25  
26 348 factor and time as the within-individual factor will be performed for outcome measures  
27  
28 349 analyses. Nonsphericity correction will be conducted using the Greenhouse-Geisser correction  
29  
30 350 if necessary, and Tukey's *post hoc* multiple comparison test will be applied.  
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37 352 ***Patient and public involvement***

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39 353 Patients and the public will not be involved in the study design, recruitment, implementation  
40  
41 354 or reporting. However, the study results will be disseminated to the public through academic  
42  
43 355 papers and conferences.  
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49 357 **Ethical approval, trial registration and dissemination**

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51 358 The study was approved by the West China Hospital Clinical Trials and Biomedical Ethics  
52  
53 359 Committee of Sichuan University on May 19, 2022 (ethics reference: 2022 (573)), and will be  
54  
55 360 conducted in accordance with the Declaration of Helsinki.  
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58 361 This protocol was registered on November 3rd, 2022, in the Chinese Clinical Trial Registry  
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3 362 with the registration number ChiCTR2200065369. This trial is a sub-project of the National  
4  
5 363 Natural Science Foundation of China with the registration number is ChiCTR2200061225.  
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7  
8 364 All participants will be fully informed of the study procedures and sign the informed consent  
9  
10 365 form voluntarily before inclusion (see the Appendix). The private information of all  
11  
12 366 participants will be kept confidential and securely placed in a locked cabinet and will only be  
13  
14 367 accessible to researchers of the study. However, the results of this study will be published in  
15  
16 368 peer-reviewed journals and disseminated at academic conferences.  
17  
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19 369

## 21 370 **Discussion**

23  
24 371 At present, no research has revealed the effect and potential mechanism of cerebellar vermis  
25  
26 372 iTBS on balance in patients with subacute stroke. This prospective single-centre double-blind  
27  
28 373 randomized controlled clinical trial with a 3-week intervention and 3-week follow-up is  
29  
30 374 designed to confirm its effectiveness.  
31  
32  
33 375 Our study will comprehensively assess trunk control and balance function by clinical scales,  
34  
35 376 balance tests via the Smart Equitest Balance Master System and sEMG measurements.  
36  
37  
38 377 Additionally, we will also collect the concentration of HbO<sub>2</sub> in the cerebral cortex via resting-  
39  
40 378 state fNIRS. The integrated data results will be sufficient verify the research hypothesis.  
41  
42  
43 379 For trunk control, the TIS scores can reveal motor impairment of the trunk in patients with  
44  
45 380 stroke. The sEMG signal directly reflects the activation of muscles directly and contains  
46  
47 381 information about movement intentions generated by the brain.<sup>50</sup> AEMG represents the  
48  
49 382 degree of muscle activation and the synchronization of activated motor units. RMS quantifies  
50  
51 383 the effort of the muscle. MPF and MF are frequency domain features and indicate muscle  
52  
53 384 fatigue.<sup>51 52</sup>  
54  
55  
56 385 For balance function, the BBS score reflects the overall performance of static and dynamic  
57  
58 386 balance. Accurate integration of sensory information is critical to maintaining balance. The  
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3 387 composite equilibrium score of the SOT characterizes the impairments of individual sensory  
4  
5 388 systems.<sup>53</sup> The ability to voluntarily move the COG within the LOS is fundamental to  
6  
7 389 mobility tasks. By the LOS test, reaction time, movement velocities and excursions are  
8  
9 390 recorded to measure the voluntary ability to shift the COG without losing balance. Reaction  
10  
11 391 time reflects the cognitive processing ability. Movement velocities indicate high-level central  
12  
13 392 nervous system function. Excursions can be restricted by biomechanical deficits.<sup>54</sup> Overall,  
14  
15 393 limitations in the LOS are associated with instability during weight-shifting activities. RWS  
16  
17 394 measures movement velocity and directional control during rhythmic movements. Patients  
18  
19 395 with disrupted normal rhythmic movement control exhibit reduced velocities and/or poor  
20  
21 396 directional control ability.<sup>55</sup>  
22  
23  
24 397 For cortical activation, fNIRS is a widespread noninvasive measurement that provides real-  
25  
26 398 time monitoring of haemodynamic signals to reflect changes in brain activation.<sup>56</sup> Increased  
27  
28 399 HbO<sub>2</sub> is positively correlated with cortical excitability. In addition, balance function and  
29  
30 400 postural stability are positively related to the changes in HbO<sub>2</sub> signals in the bilateral SMAs  
31  
32 401 in patients with stroke.<sup>57</sup> Additionally, our previous work revealed that single-session  
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34 402 cerebellar vermis iTBS can increase bilateral SMAs excitability during balance tasks in  
35  
36 403 healthy adults.<sup>23</sup>  
37  
38 404 We hypothesize that cerebellar vermis iTBS can promote the activation of muscles in the  
39  
40 405 trunk and lower limbs, and increase the excitability of the SMAs to improve trunk control and  
41  
42 406 balance function in patients after stroke. The cerebellar vermis plays an important role in  
43  
44 407 postural tone, balance, and locomotion through descending spinal pathways since the vermis  
45  
46 408 receives vestibulocerebellar and proprioceptive spinocerebellar afferents.<sup>58</sup> SMA contributes  
47  
48 409 to anticipatory postural adjustments and postural stability during gait initiation.<sup>59</sup> iTBS  
49  
50 410 consists of high-frequency stimulation bursts that strongly modulate the neural activity of the  
51  
52 411 cerebellar vermis. Studies with humans have shown that iTBS drives acute changes to motor  
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3 412 behaviour and neuronal excitability.<sup>60</sup> A possible mechanism has been reported by an animal  
4  
5 413 study showing that iTBS can promote neural structural remodelling and functional recovery  
6  
7 414 by enhancing neurogenesis and migration via the miR-551b-5p/BDNF/TrkB pathway.<sup>61</sup> The  
8  
9 415 first study of cerebellar vermis stimulation was reported in 1995, which investigated its  
10  
11 416 effects on saccade metrics in a man via TMS.<sup>62</sup> At present, researchers have reported that  
12  
13 417 cerebellar vermis stimulation is a safe and well-tolerated brain stimulation technology with a  
14  
15 418 potential therapeutic effect on schizophrenia.<sup>63</sup> In addition, cerebellar vermis rTMS can  
16  
17 419 induce a suppressive effect on pharyngeal motor cortical activity and swallowing behaviour.<sup>64</sup>  
18  
19 420 However, limited studies have reported that the cerebellar vermis plays an important role in  
20  
21 421 postural response and balance stability.<sup>13 65</sup> Therefore, we hope to identify the effectiveness of  
22  
23 422 cerebellar vermis iTBS in trunk control and balance function for patients with subacute  
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25 423 ischemic stroke. Our results may provide valuable information for developing a novel  
26  
27 424 treatment method for the rehabilitation of balance dysfunction after stroke.  
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33 425  
34  
35 426 **Author contributions:** Conceptualization, validation, and original draft: YC.  
36  
37 427 Recruitment: LH, HHJ, and QCW. Data collection: YC, WS, and HXT. Data analysis: CFG  
38  
39 428 and QFG. Manuscript review and editing: CFG and QG. QG designed the trial and was  
40  
41 429 responsible for the manuscript. All authors read and approved the final manuscript.  
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48  
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52 433  
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54 434 **Conflict of Interest:** None.  
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3 436 **Acknowledgments:** None.  
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7 438

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5 **637 Figure 1.** The flow diagram of the study design.  
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7 **638 Figure 2.** The schedule of enrolment, interventions, and assessments.  
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9 **639 Figure 3.** The Magstim Rapid2 stimulator with a BrainSight neuronavigation system.  
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11 **640 Figure 4.** The Smart Equitest Balance Master System®.  
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13 **641 Figure 5.** The sensor locations on individual muscles for sEMG recording (A. rectus  
14 abdominis, B. external oblique muscle, C. rector spinae (longissimus), D. rectus femoris, E.  
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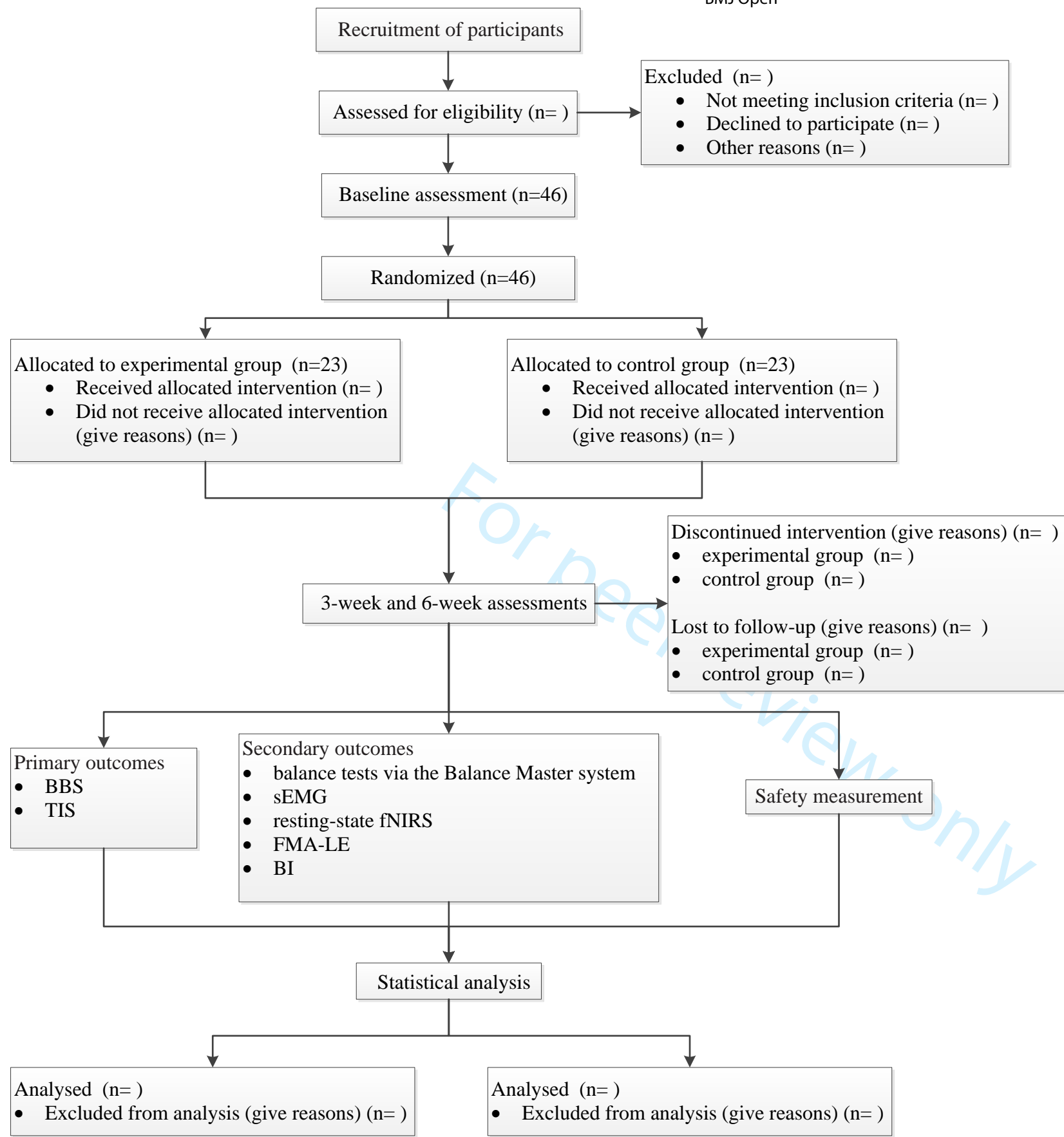
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**Enrollment**

**Intervention**

**Assessment**

**Analysis**





**Figure 2.** The schedule of enrolment, interventions, and assessments.

	Enrolment	Allocation	Post-allocation					
TIMEPOINT	$-t_1$	0	W1	W2	W3	W4	W5	W6
<b>ENROLMENT:</b>								
Eligibility screen	X							
Informed consent	X							
Ethical approval and trial registration	X							
Allocation		X						
<b>INTERVENTIONS:</b>								
cerebellar vermis iTBS and conventional physical therapy			↔					
sham stimulation and conventional physical therapy			↔					
<b>ASSESSMENTS:</b>								
basic characteristics information		X						
BBS		X			X			X
TIS		X			X			X
balance tests via the Balance Master system		X			X			X
sEMG		X			X			X
resting-state fNIRS		X			X			X
FMA-LE		X			X			X
BI		X			X			X
Safety measurement			X	X	X	X	X	X

W, week; iTBS, intermittent theta-burst stimulation; BBS, Berg balance scale; TIS, trunk impairment scale; sEMG, surface electromyography; fNIRS, functional near-infrared spectroscopy; FMA-LE, Fugl-Meyer assessment scale score for lower extremities; BI, Barthel index.

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Figure 3. The Magstim Rapid2 stimulator with a BrainSight neuronavigation system.

1066x1422mm (72 x 72 DPI)



Figure 4. The Smart Equitest Balance Master System®.

1066x1422mm (72 x 72 DPI)

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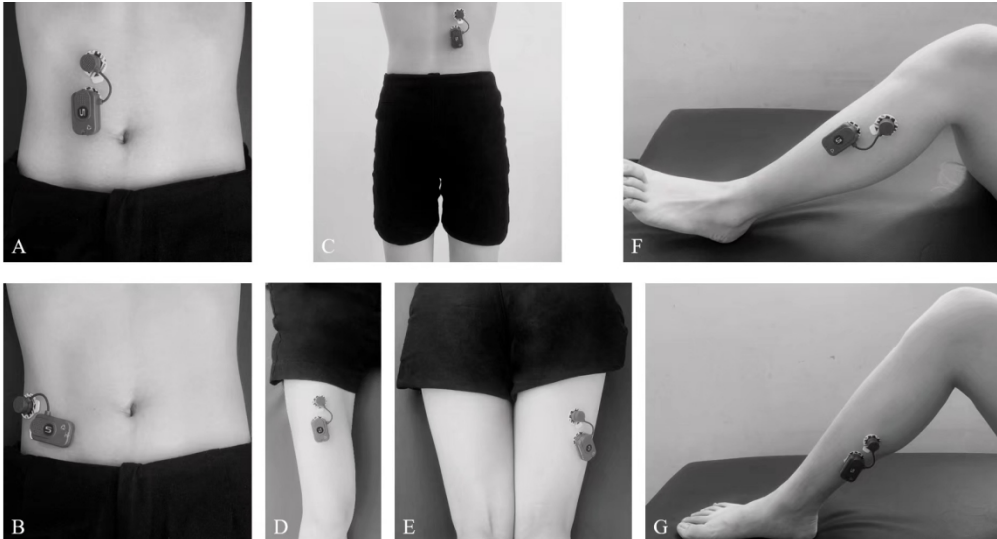


Figure 5. The sensor locations on individual muscles for sEMG recording (A. rectus abdominis, B. external oblique muscle, C. rector spinae (longissimus), D. rectus femoris, E. biceps femoris, F. tibialis anterior, G. soleus)

654x359mm (72 x 72 DPI)

**Appendix.** Informed Consent Form

<b>West China Hospital, Sichuan University</b>			
<b>Participant Informed Consent</b>			
<b>Name:</b>	<b>Gender:</b>	<b>Age:</b>	<b>Inpatient ID:</b>
<p><b>Title of study:</b> The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for patients with subacute stroke: a randomized controlled trial</p> <p><b>Investigator:</b> Qiang Gao</p> <p><b>Funding:</b> NSFC 82172540 from the National Natural Science Foundation of China</p> <p><b>What is the study about?</b></p> <p>(1) The aim of the study is to determine the effects of cerebellar vermis intermittent theta-burst stimulation (iTBS) on trunk control, muscle activation and balance function in stroke patients. We will recruit 46 patients who meet the inclusion criteria as follows: (1) a diagnosis of ischemic stroke according to the <i>Diagnostic criteria of cerebrovascular diseases in China (version 2019)</i>, (2) aged between 18 and 65 years, (3) first-ever unilateral ischemic stroke confirmed by imaging examination, (4) subacute stroke participants with the stroke onset ranging from 2 weeks to 6 months, (5) having motor deficit and balance dysfunction, with a Fugl-Meyer Assessment for Lower Extremities (FMA-LE) &lt;34 points and BBS score &lt;56 points. Patients were excluded if they presented one of the following: (1) diagnosis of coexisting other neurological diseases, (2) injury of cerebellar or brain stem, (3) having contraindications for iTBS (e.g., history of seizures, intracranial metallic implants, microprocessor implants in the body, tumours, and pregnancy), (4) cognitive impairment with a Mini-Mental State Examination (MMSE) score &lt;27, (5) treatment with benzodiazepines, baclofen, antiepileptics and antidepressants.</p>			

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4 ***How long will I be in the study?***  
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6 Your part in the study will last **6 weeks** with 3 weeks of intervention and 3 weeks of  
7 follow-up (excluding assessment).  
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11 ***What will happen in this study?***  
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13 You will be randomized into either the experimental or control group according to  
14 the random number table. If you assigned to the experimental group will receive  
15 cerebellar vermis iTBS after routine daily conventional physical therapy, otherwise  
16 you will receive sham stimulation after routine daily conventional physical therapy.  
17 The overall intervention periods are five days a week for three consecutive weeks.  
18 You will be assessed before treatment, after 3 weeks of intervention and after 3  
19 weeks of follow-up. The measures including clinical scales, balance tests via the  
20 Balance Master system, and the surface electromyography recording.  
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31 If you are eligible and wish to join the study, you must sign this consent form. If  
32 you do not sign the consent form you cannot join the study.  
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36 We will review this consent form with you. You will be given enough time to  
37 review the consent and have all your questions about the study answered. We will  
38 give you a signed copy of the consent for your records before treatment in person.  
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44 Study staff will not know which group or study treatment you are assigned to. You  
45 should not join the study if you are not willing to take the study treatment (or join  
46 the group) you are assigned to.  
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52 ***What if I have questions?***  
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54 You can contact the therapist at working hours if you have questions about the  
55 study. Qiang Gao (the director of therapists) is in charge of the study.  
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***Do I have to be in the study?***

You decide if you want to be in the study. Deciding not to take part will not affect your relationship with your therapist. If your therapist is an investigator for the study, you may get a second opinion from another therapist not involved in the study.

You can leave the study at any time and you do not have to give a reason. Leaving the study will not affect your relationship with your therapist.

The study investigators may ask you to leave the study if it is in your best interest.

The study investigator may ask you to leave the study if you do not follow the study rules.

***What if I don't want to be in the study?***

You can choose not to be in the study and you do not have to give a reason. You can choose to (talk to your doctor/therapist about other options, investigate outside resources on your own, etc.).

***Are there any costs?***

All study-related treatments are free.

***Will I be paid for being in the study?***

You will not be paid for being in the study.

***Are there any risks?***

There is always a small risk of a breach of confidentiality to your personal health information. However, these risks have been addressed and minimized as much as is possible.

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4 You will be told about any new information that may affect your willingness to  
5 participate in the study.  
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9 There are some possible risks and side effects as follows: headache, nausea, neck  
10 pain, seizure, mood changes, fatigue, tinnitus, dizziness, sleepiness and syncope.  
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15 If you experience any side effects while on the study contact investigator (Qiang  
16 Gao) at any time as soon as possible.  
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21 ***What if I feel I've been hurt by taking part in the study?***  
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23 If you feel you have been injured or harmed by taking part in this study, please  
24 contact investigator (Qiang Gao) at any time. If you feel you were harmed while  
25 taking part in this study, you may be treated at West China Hospital, Sichuan  
26 University. However, West China Hospital does not offer to pay the cost of this  
27 treatment.  
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32 If you feel your rights have been violated or you have harmed by this study, please  
33 contact your therapist.  
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38 ***Are there any benefits?***  
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41 It is possible you may receive some benefit from cerebellar vermis iTBS and  
42 conventional physical therapy. iTBS is a novel form of rTMS, which can produce  
43 long-term potentiation and is more rapid and efficacious than standard rTMS.  
44  
45 Cerebellar vermis is a cardinal structure involved in balance and motor control,  
46 which is responsible for regulating the trunk, head, neck and proximal limb muscles  
47 to control posture and maintain balance. There is no guarantee, however, that you  
48 will receive any benefit at all. Your participation will help us learn more about the  
49 effects of cerebellar vermis iTBS on trunk control, muscle activation and balance  
50 function in subacute stroke patients.  
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***Your privacy is important***

Protecting your privacy is very important to us.

During this study we will ask about your (past) and (current) medical history. This information will be used to determine your eligibility for the study and provide data for the study. Your personal health information will be kept private and only authorized study staff will have access to this information. We will use a study number instead of your name. All paper forms will be kept in a locked, secure office. All electronic data will be stored on password-protected computers. Your name will not be used in any publications or presentations about this study.

During the study, you may not be given access to medical information about you that is part of the study. When the study is over, you may request certain medical information collected about you that is part of your study medical record.

None of your personal information will be shared outside of West China Hospital.

By signing this consent form, you are stating that we can use your health information in the ways mentioned above for this study. You are not waiving any of your legal right by signing this form.

You have the right to take away your permission to use your health information collected as part of the study. In order to do this, you must send a written request to: Qiang Gao, department of rehabilitation, West China hospital, Sichuan University

Once your letter is received, no additional information about you will be collected from you for this study. Any data that were collected before we receive your letter will continue to be used for the study. Taking away your permission to use your

health information will not affect your relationship with West China Hospital.

We are collecting only the personal health information that we need for the specific purpose of this study. Your personal health information cannot be used for additional research purpose.

The West China hospital may be required to provide copies of your personal information to government agencies as required by law.

Your permission to use your identifiable health information when the study is complete.

***Signatures:***

By signing this consent form, it means the following:

- I know my rights have not been waived by signing.
- I have had all of my questions answered and I know whom to ask if I have more questions.
- I have read this form and understand it.
- I want to join the study.
- I know I can leave the study at any time and do not have to give a reason.

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Date



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

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Section/item	Item No	Description	Page
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 17-18
	2b	All items from the World Health Organization Trial Registration Data Set	nil
Protocol version	3	Date and version identifier	nil
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, 20
	5b	Name and contact information for the trial sponsor	Title page
	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	20
	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)	nil
<b>Introduction</b>			
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	3-5
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6

## Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-6, Fig.2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6

## Methods: Assignment of interventions (for controlled trials)

Allocation:

1	Sequence	16a	Method of generating the allocation sequence (eg,	16
2	generation		computer-generated random numbers), and list of any	
3			factors for stratification. To reduce predictability of a random	
4			sequence, details of any planned restriction (eg, blocking)	
5			should be provided in a separate document that is	
6			unavailable to those who enrol participants or assign	
7			interventions	
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg,	16
11	concealment		central telephone; sequentially numbered, opaque, sealed	
12	mechanism		envelopes), describing any steps to conceal the sequence	
13			until interventions are assigned	
14				
15	Implementation	16c	Who will generate the allocation sequence, who will enrol	16
16			participants, and who will assign participants to interventions	
17				
18				
19	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg,	16
20			trial participants, care providers, outcome assessors, data	
21			analysts), and how	
22				
23		17b	If blinded, circumstances under which unblinding is	16
24			permissible, and procedure for revealing a participant's	
25			allocated intervention during the trial	
26				
27				
28	<b>Methods: Data collection, management, and analysis</b>			
29				
30	Data collection	18a	Plans for assessment and collection of outcome, baseline,	16
31	methods		and other trial data, including any related processes to	
32			promote data quality (eg, duplicate measurements, training	
33			of assessors) and a description of study instruments (eg,	
34			questionnaires, laboratory tests) along with their reliability	
35			and validity, if known. Reference to where data collection	
36			forms can be found, if not in the protocol	
37				
38				
39		18b	Plans to promote participant retention and complete follow-	16-17
40			up, including list of any outcome data to be collected for	
41			participants who discontinue or deviate from intervention	
42			protocols	
43				
44				
45	Data management	19	Plans for data entry, coding, security, and storage, including	16
46			any related processes to promote data quality (eg, double	
47			data entry; range checks for data values). Reference to	
48			where details of data management procedures can be	
49			found, if not in the protocol	
50				
51				
52	Statistical methods	20a	Statistical methods for analysing primary and secondary	17
53			outcomes. Reference to where other details of the statistical	
54			analysis plan can be found, if not in the protocol	
55				
56		20b	Methods for any additional analyses (eg, subgroup and	17
57			adjusted analyses)	
58				
59				
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1		20c	Definition of analysis population relating to protocol non-	17
2			adherence (eg, as randomised analysis), and any statistical	
3			methods to handle missing data (eg, multiple imputation)	
4				
5	<b>Methods: Monitoring</b>			
6				
7	Data monitoring	21a	Composition of data monitoring committee (DMC); summary	16
8			of its role and reporting structure; statement of whether it is	
9			independent from the sponsor and competing interests; and	
10			reference to where further details about its charter can be	
11			found, if not in the protocol. Alternatively, an explanation of	
12			why a DMC is not needed	
13				
14				
15		21b	Description of any interim analyses and stopping guidelines,	16
16			including who will have access to these interim results and	
17			make the final decision to terminate the trial	
18				
19	Harms	22	Plans for collecting, assessing, reporting, and managing	15-16
20			solicited and spontaneously reported adverse events and	
21			other unintended effects of trial interventions or trial conduct	
22				
23				
24	Auditing	23	Frequency and procedures for auditing trial conduct, if any,	16-18
25			and whether the process will be independent from	
26			investigators and the sponsor	
27				
28				
29	<b>Ethics and dissemination</b>			
30				
31	Research ethics	24	Plans for seeking research ethics committee/institutional	17-18
32	approval		review board (REC/IRB) approval	
33				
34	Protocol	25	Plans for communicating important protocol modifications	nil
35	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
36			relevant parties (eg, investigators, REC/IRBs, trial	
37			participants, trial registries, journals, regulators)	
38				
39				
40	Consent or assent	26a	Who will obtain informed consent or assent from potential	18
41			trial participants or authorised surrogates, and how (see	
42			Item 32)	
43				
44		26b	Additional consent provisions for collection and use of	not applicable
45			participant data and biological specimens in ancillary	
46			studies, if applicable	
47				
48				
49	Confidentiality	27	How personal information about potential and enrolled	18
50			participants will be collected, shared, and maintained in	
51			order to protect confidentiality before, during, and after the	
52			trial	
53				
54	Declaration of	28	Financial and other competing interests for principal	20
55	interests		investigators for the overall trial and each study site	
56				
57				
58	Access to data	29	Statement of who will have access to the final trial dataset,	16-18
59			and disclosure of contractual agreements that limit such	
60			access for investigators	

1	Ancillary and post-	30	Provisions, if any, for ancillary and post-trial care, and for	nil
2	trial care		compensation to those who suffer harm from trial	
3			participation	
4				
5	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial	17-18
6			results to participants, healthcare professionals, the public,	
7			and other relevant groups (eg, via publication, reporting in	
8			results databases, or other data sharing arrangements),	
9			including any publication restrictions	
10				
11				
12		31b	Authorship eligibility guidelines and any intended use of	nil
13			professional writers	
14				
15		31c	Plans, if any, for granting public access to the full protocol,	nil
16			participant-level dataset, and statistical code	
17				
18				
19	<b>Appendices</b>			
20				
21	Informed consent	32	Model consent form and other related documentation given	Supplementary
22	materials		to participants and authorised surrogates	material
23				
24	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of	not applicable
25			biological specimens for genetic or molecular analysis in the	
26			current trial and for future use in ancillary studies, if	
27			applicable	
28				

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.