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# BMJ Open

## The effect and safety of neurotomy of C7 nerve at intervertebral foramen in patients of chronic aphasia after stroke: study protocol for a multicentre, randomized, controlled study

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Manuscripts

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3 1 **TITLE PAGE**  
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6 2 **The effect and safety of neurotomy of C7 nerve at**  
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8 3 **intervertebral foramen in patients of chronic**  
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10 4 **aphasia after stroke: study protocol for a**  
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12 5 **multicentre, randomized, controlled study**  
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50 36 **Keywords:** chronic aphasia after stroke, neurotomy of C7 nerve at intervertebral foramen (NC7),  
51 37 intensive speech and language therapy (iSLT), neuroplasticity  
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## ABSTRACT

- **Introduction** Aphasia affects a great number of stroke survivors, and effective treatments are urgently needed. The preliminary clinical findings implied an association between Contralateral C7 to C7 Cross Nerve Transfer (CC7) and recovery of chronic aphasia. The evidence to support the efficacy of neurotomy of C7 is unsatisfactory so far given the lack of RCT. This study aims to explore the efficiency of neurotomy of C7 nerve (NC7) at intervertebral foramen on improving chronic aphasia after stroke.
- **Methods and analysis** This study protocol reports a multicentre, randomized, controlled trial. A total of 50 patients with chronic aphasia after stroke (onset time  $\geq$  12 months, aphasia quotient of WAB score  $\leq$  93.8) will be recruited. Participants will be randomly assigned to one of two groups (n=25, respectively) to receive NC7 plus intensive speech and language therapy (iSLT) or iSLT alone programme. Since the study design does not allow participant blinding, the outcome assessor and the statistician will be blinded. The primary outcome is the change from baseline in BNT scores to post-intervention. The secondary outcomes include: aphasia quotient of WAB score, ICF assessment, CADL scale, ADL score, HRSD-24 score and other surgical safety outcomes. The study also explores the functional imaging outcomes of naming test and semantic violation that could reflect intervention-induced neuroplasticity.
- **Ethics and dissemination** This study has been approved by the Institutional Review Board of Huashan Hospital, Fudan University (No. KY2021-592), and by the IRBs of all the participating facilities. The findings will be disseminated through peer-reviewed publications and conference presentations.
- **Trial registration:** ChiCTR2200057180

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## 65 **ARTICLE SUMMARY**

### 66 **Strengths and limitations of this study**

- 67 • The results from this randomised controlled trial will provide new evidence of the efficacy and  
68 safety of NC7 for patients with chronic aphasia after stroke.
- 69 • Findings from this trial may provide a novel perspective on intervention of aphasia treatment  
70 with the underlying neuroplasticity of peripheral and central nervous system.
- 71 • One limitation is that the mechanism of neuroplasticity needs to be further studied in animal  
72 experiments.

73  
For peer review only

## 74 INTRODUCTION

### 75 Background and rationale

76 Aphasia refers to the collection of acquired receptive and expressive language deficits, which arises  
8  
9 77 in many neurological diseases or trauma, but most frequently observed following left hemisphere  
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11 78 stroke<sup>1</sup>. More than 10 million new cases of stroke are reported globally each year<sup>2</sup>, and at least one  
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13 79 third of these patients will have symptoms of aphasia<sup>3</sup>. Actually, aphasia is one of the most  
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15 80 devastating symptoms in stroke survivors<sup>4 5</sup>, which costs substantially the individuals with stroke  
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17 81 during the acute and chronic care, moreover, is an independent predictor of subsequent functional  
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19 82 dependence and death<sup>3 6</sup>. Simultaneously, the presence of aphasia predicts the needs of care and  
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21 83 rehabilitation services<sup>7</sup> and the likelihood of failure to return to work<sup>8</sup>, and increases the burden that  
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23 84 aphasia takes to the family and society.

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25 85 Language is an indispensable part of cognitive function, and affects patients' attention,  
26  
27 86 comprehension and other functions<sup>9</sup>. Aphasia, impairment of language after stroke or other  
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29 87 neurological insult, is a common and often devastating condition that affects nearly every social  
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31 88 activity and interaction. The language function of the patients will recover spontaneously to varying  
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33 89 degrees<sup>10</sup>. The traditional view is that language function will reach the chronic phase at 6-9 months  
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35 90 after stroke, and with few changes later<sup>11 12</sup>. During recovery, both the subtype and severity of  
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37 91 aphasia change over time, and patients may progress from sensory aphasia to conduction aphasia to  
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39 92 naming aphasia to "recovered"<sup>13</sup>, although this "recovered" may also have mild residual impairment  
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41 93 that could be detected by a more sensitive assessment<sup>14</sup>. However, some forms of aphasia persists  
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43 94 into the chronic phase in half of patients at least<sup>15</sup>.

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45 95 Although most aphasia therapy studies have enrolled chronic patients, it seems likely that earlier  
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47 96 aphasia therapy is also effective, which has achieved good results in improving aphasia after  
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49 97 stroke<sup>16</sup>. Common aphasia rehabilitation treatments include classic speech-language rehabilitation  
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51 98 training, as well as low-frequency electrical stimulation therapy, repetitive transcranial magnetic  
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53 99 stimulation and transcranial direct current stimulation. A large number of clinical studies<sup>17 18</sup> have

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3 100 shown that speech and language therapy (SLT) is effective in improving communication, reading,  
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5 101 writing, and language expression in post-stroke aphasia patients, while the high-intensity, and  
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8 102 long-term mode may has better effects<sup>19</sup>. A large-scale RCT study showed that<sup>18</sup>, the 3 weeks  
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10 103 intensive speech and language therapy (iSLT) would be proven the effects for patients with chronic  
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12 104 aphasia after stroke, which significantly enhanced verbal communication among people aged 70  
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15 105 years or younger, and this benefit could be maintained until 6 months after treatment. Stahl<sup>20</sup> further  
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17 106 determined the optimal daily dosage and total duration of iSLT. The results showed no added value  
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19 107 from more than 2 hours of daily SLT within 4 weeks. In addition, non-invasive brain stimulation  
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22 108 therapy is widely used in the rehabilitation of various neurological diseases. Transcranial direct  
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24 109 current stimulation (tDCS) uses electrode pads to deliver a weak direct current to specific brain  
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26 110 regions of patients, which can affect the function of the cerebral cortex and help improve the  
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28 111 accuracy of noun naming in patients with aphasia<sup>21-23</sup>. However, there is still a lack of enough  
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31 112 sample size and strict methodology. Low-frequency repetitive transcranial magnetic stimulation  
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33 113 (rTMS) is the regular and repeated application of a pulsed magnetic field that briefly penetrates the  
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35 114 skull to specific cortical regions, which induces plastic changes in brain and language function in  
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38 115 long-term post-stroke aphasia patients, but its efficacy is still controversial and needs to be further  
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40 116 confirmed by large-scale clinical trials<sup>24</sup>.

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42 117 We previously developed a surgical procedure for contralateral seventh cervical nerve transfer from  
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45 118 the nonparalyzed side to the paralyzed side(contralateral C7 to C7 cross nerve transfer, CC7), after  
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47 119 which patients demonstrated improved motor function and reduced spasticity in the paralyzed arm  
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49 120 over 12 months<sup>25</sup>. So far more than 1,000 patients have undergone the surgery<sup>26</sup>, in addition to arm  
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51 121 motor recovery, the improvement of language was frequently self-reported by patients and  
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54 122 caregivers during the following-up process, and it would occur very rapidly after CC7 treatment. A  
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56 123 few days is far from enough time for the transferred C7 nerve to regenerate<sup>27</sup>, thus we assumed that  
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58 124 the rapid improvement of language function was mediated by the neurotomy C7 nerve on the  
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3 125 paralyzed side (right side), rather than nerve regeneration. During the CC7 operation<sup>28</sup>, to make the  
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5 126 C7 nerve on the paralyzed side provide more length of nerve fibres, we cut the C7 nerve root at  
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8 127 intervertebral foramen. Based on anatomical research, the anterior and posterior roots converge into  
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10 128 spinal nerves at the intervertebral foramen, and the posterior roots enlarge near the intervertebral  
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12 129 foramen to form ganglia, also known as dorsal root ganglion (DRG)<sup>29 30</sup>. The exact location of  
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14 130 neurotomy is at the transitional junction of the C7 nerve root with DRG<sup>31</sup>. In most cases, aphasia is  
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17 131 caused by strokes involving the left hemisphere, with more extensive damage typically being  
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19 132 associated with more severe aphasia.<sup>32</sup> Based on the anatomy of brain functional areas, since the  
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22 133 motor centre is adjacent to the language centre, if the motor centre can be changed artificially, it's  
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24 134 possible to induce the language centre and produce related functional changes. Human C7 nerve  
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26 135 contains 80,000 fibers<sup>33</sup>, 94% of which are sensory fibres emitted by DRG<sup>34</sup>. Hence, the neurotomy  
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29 136 of C7 nerve root with DRG can block the sensory ascending pathway from the affected limb to the  
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31 137 brain. Therefore, we speculate that the clinical phenomenon of language function improvement is  
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33 138 due to the stimulation inducing neuroplasticity of the "language centre", that is, "Reconstructing the  
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35 139 peripheral nerve changes the central nervous system." To confirm our hypothesis, we designed this  
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38 140 trial to evaluate the surgical effect of neurotomy of C7 nerve at intervertebral foramen (NC7) on  
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40 141 underlying neuroplasticity in patients with chronic aphasia after stroke. Meanwhile, the iSLT is  
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42 142 selected as the intervention method of control group, and will evaluate the effect of intensive  
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45 143 intervention after 3 weeks and the maintenance effect after 6 months of the both groups  
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47 144 respectively.

### 51 146 **Aims of the study**

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53 147 The study aims to evaluate the therapeutic efficacy of the neurotomy of C7 nerve at intervertebral  
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55 148 foramen on language impairment in patients with chronic aphasia after stroke. The current paper  
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57 149 describes the design of this study.

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59 150 Specific objectives are: (1) to evaluate the comparative effectiveness of different interventions, NC7



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3 151 plus intensive speech and language therapy (3 weeks) and intensive speech and language therapy (3  
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6 152 weeks) alone, and the further validation of the safety and long-term (6 months) effectiveness of  
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8 153 NC7 surgical programme. (2) to evaluate the motor and sensorimotor function of paralyzed arm,  
9  
10 154 clarify the correlation between motor function and language function changes, postoperatively. (3)  
11  
12 155 to confirm the central mechanism of neurotomy of C7 nerve at intervertebral foramen and access  
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14  
15 156 the underlying neuroplasticity via functional neuroimaging measurements.  
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## 18 **METHODS/DESIGN**

### 19 158 **Trial design**

20  
21 159 This study is a multicenter, randomized controlled trial with two parallel groups and 6-month  
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23 160 follow-up. Based on language and motor function analysis, the protocol that compares patients with  
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25 161 chronic aphasia treated with the neurotomy of C7 nerve at intervertebral foramen (NC7) and  
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27 162 intensive speech and language therapy (iSLT) (Group A), with a control group participating in iSLT  
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29 163 alone (Group B). The participants involved will be randomly allocated to one of two groups  
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31 164 (NC7+iSLT group or iSLT group) with a ratio of 1:1. The study is conducted in collaboration of the  
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33 165 Speech Therapy Committee of Shanghai Association of Rehabilitation Medicine (STCSARM), and  
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35 166 the participants will be collected from rehabilitation facilities of this organization. Ethical approval  
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37 167 for this trial was granted by the Institutional Review Board of Huashan Hospital, Fudan University  
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39 168 (HIRB), and by the IRBs of the all participating facilities. Patients who will receive an indication  
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41 169 for outpatient rehabilitation treatment at any of four centres, based on the eligibility criteria listed  
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43 170 below. The potentially eligible patients will be invited to participate via a text message after signing  
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45 171 the informed consent.  
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### 53 54 174 **Eligibility criteria**

#### 55 175 ***Inclusion criteria:***

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59 176 1) Aphasia for over 12 months after single onset of infarction or hemorrhage of the left hemisphere  
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3 177 which is confirmed by magnetic resonance imaging;

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5 178 2) 40-65 years old, male or female, right-handed, native Chinese speaker;

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7 179 3) Aphasia quotient below 93.8 points assessed by Western Aphasia Battery;

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9 180 4) The severity assessed by BDAE test: level 1 and above;

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11 181 5) Good compliance and can cooperate with language rehabilitation training;

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13 182 6) The subjects can fully understand and agree with the doctor's treatment plan and sign the

14

15 183 informed consent.

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17 184 Points 3 and 4 need to be confirmed by two attending specialists' agreements on diagnosis.

18

19 185 **Exclusion criteria:**

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21 186 1) Surgical contraindications for any reason judged by a qualified anesthesiologist or clinician;

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23 187 2) Patients with a history of aphasia before the last onset of the stroke;

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25 188 3) Suffering from serious, untreated mental illness;

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27 189 4) Aphasia due to neurodegenerative diseases or traumatic brain injury;

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29 190 5) The subjects have contraindications for EEG and MRI detection;

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31 191 6) Unable to complete the assessments and rehabilitation required by the study design;

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33 192 7) Severe motor speech disorder and hearing impairment;

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35 193 8) Received intensive post-stroke rehabilitation therapy 4 weeks before recruitment.

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## 39 195 **Interventions**

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### 41 196 **Neurotomy of C7 nerve at intervertebral foramen**

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43 197 Make a 6-cm long longitudinal incision along the medial border of the sternocleidomastoid muscle

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45 198 on right side after cervical plexus anesthesia/general anesthesia (depend on patient preference and

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47 199 through risk assessment by anesthesiologist), carefully separate the structure layer by layer and

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49 200 identify the brachial plexus by marking the C7 nerve with a vessel loop. The C7 root is mobilized

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51 201 and sectioned as proximally (at intervertebral foramen) as possible. Considering that some patients

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53 202 have limb hemiplegia, CC7 surgery may be required to improve limb function at the end of this

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3 203 trial. Therefore, we fixed the severed C7 root to the fascia at the junction of the scapulothyoid and  
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5 204 sternocleidomastoid muscles with silk thread, making it easier to find and then anastomosed with  
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8 205 the contralateral C7 root during the later CC7<sup>28</sup> surgical programme.  
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### 11 12 207 **iSLT Rehabilitation**

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15 208 With reference to the previous studies, we formulated a 3-week iSLT plan. Speech and language  
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17 209 therapy with a therapist at least 45 minutes/time, twice per day, 5 days/week. Additional 1 hour/day  
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19 210 self-administrated language-specific training. For arm motor, the rehabilitation therapy based on the  
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22 211 Brunnstrom principle is provided. Rehabilitation includes active exercise, passive range of motion  
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24 212 training, occupational therapy, functional training, physical therapy, acupuncture, massage and the  
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26 213 use of orthotics. Patients receive rehabilitation treatment at different study centres, where qualified  
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28 214 rehabilitation therapists perform the therapy.  
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### 32 33 216 **Study setting**

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35 217 A total of 50 patients with diagnosed aphasia with hemiplegia after chronic stroke will be recruited.  
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37 218 Patients will receive hospitalized treatment over a period of 3-4 weeks in the research institutions,  
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40 219 with follow-up assessment at 6 months after start of treatment (Figure1). On their first visit, patients  
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42 220 will be selected for study eligibility according to the inclusion and exclusion criteria. After this  
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44 221 baseline evaluation, eligible patients will be randomly assigned to one of the two groups according  
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47 222 to different centres. Patients of Group A receive NC7 immediately after assignment, and receive  
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49 223 short-term efficacy assessment after 3 days, the total perioperative period is one week. In the  
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51 224 meantime, patients of Group B are waiting for therapy programme. Then, the iSLT and upper  
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53 225 extremity motor rehabilitation programme are provided for patients in both groups. After a 3-week  
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56 226 inpatient invention, all the patients received primary endpoint assessments, then they continue to  
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58 227 receive conventional low-intensity SLT at home or in other centres. For arm motor, patients are  
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228 guided to consistently keep the rehabilitation, and the therapy intensity and duration are recorded by  
229 the therapist or caregiver. Six months later, the second visit, all the patients will receive interim  
230 evaluation by trained therapist belonging to an independent team. Afterwards, the NC7 and  
231 postoperative rehabilitation programme (both of iSLT and motor rehabilitation) which is consistent  
232 with Group A are performed in patients of Group B. Likewise, these patients will receive a  
233 short-term and long-term follow-up for efficacy assessment. Schedule of enrolment, interventions  
234 and assessments is provided in Table 1.

### Participant timeline

The time schedule is presented in Table 1.

**Table 1. Timeline schedule of enrolment, interventions, and assessments.**

TIMEPOINT	STUDY PERIOD							
	Enrolment	Allocation	Baseline	Post-allocation			Follow-up	
		1W		2W	3-5W		2-7M	
	-T0		T0		T1		T2	T3
<b>SCREENING AND ENROLMENT</b>								
Eligibility screen	√							
Informed consent	√							
<b>INTERVENTIONS</b>								
NC7+iSLT program (Group A: experimental group)				√		√		
iSLT program (Group B: control group)						√		
No or low-intensity SLT (both groups)							√	
<b>ASSESSMENTS</b>								
Demographic variables Age, gender, education et al.	√							

<b>Primary outcomes</b>			√		√*		√★		√**
<b>Secondary outcomes</b>			√		√*		√★		√**
<b>Brain plasticity evaluation</b>			√				√★		√**
<b>Safety outcomes</b>			√		√*		√★		√**
<b>Adverse event assessment</b>					√		√		√

(W) week, from enrolment; (M) month, from enrolment; (-T0) Preparation stage before allocation; \*(T1) Short-term efficacy assessments in Group A; ★(T2-T0) Primary endpoint, from baseline to 4 weeks later in both groups; \*\*(T3) Long-term efficacy assessments in both groups.

## Randomization and blinding

The stratified block randomization process of this study is done by using an interactive web response system (IWRS), and the stratified factor is the centre (Huashan Hospital, Fudan University; Shanghai Pudong Hospital; Huadong Hospital affiliated to Fudan University, Shanghai Xuhui District Central Hospital). The blinding method of this clinical trial is applied in the outcome evaluation stage. During the onsite evaluation process, patients will be required to wear a cervical collar to cover the neck (wound site of patients in experimental group), which will be videotaped. The process of video recording and video performance scoring will be conducted by an independent team, which consists of trained therapists.

## Outcomes measures

The primary outcome is the change in total score on the Boston naming test (BNT) scale of Group A and B from baseline (T0) to post-intervention (week 4, T2). BNT is a classic measurement tool for evaluating language function, the international version is BNT-60. The BNT scale shows a high concurrent validity with other standard naming ability assessment tools, and it is particularly suitable in the post-acute/chronic phase after stroke aphasia. In this study, we choose the validated

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3 262 Chinese version of BNT<sup>35 36</sup>.

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5 263 The secondary outcomes include Aphasia quotient, daily communication (CADL-3), activities of

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8 264 daily living (Barthel Index), speech language function assessment (ICF<sup>37</sup> speech language function

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10 265 assessment), post stroke depression assessment (Hamilton Rating Scale for Depression, HRSD) and

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12 266 safety outcomes in different groups. Assessments performed to collect data for the primary,

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15 267 secondary, and safety outcomes are listed in the Table 2.

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19 269 **Table 2. Assessments performed to collect data for the primary, secondary, and safety**  
20 270 **outcomes**

Variable	Measure
<b>Primary outcome</b>	
Naming ability	Change from baseline in Boston Naming Test (BNT) score. The BNT scale is a performance-based measure commonly used to assess the visual confrontation naming ability among adults with aphasia. Participants are shown pictures of common objects and asked to name each stimulus item within 20 seconds. Minimum score 0, maximum score 60. Higher scores mean better outcome in naming ability.
<b>Secondary outcome</b>	
Aphasia quotient	Change from baseline in WAB score The WAB scale is a weighted average of all subtest scores relating to spoken language. It is a sum of all subtest scores from the first four parts of the WAB (Spontaneous speech, Auditory verbal comprehension, Repetition, Naming and word finding). Recording the total average score and standard deviation. The total range is 0-100 (higher scores indicating better performance).
Daily communication	Change from baseline in the Communication Activities of Daily Living–Third Edition (CADL-3) The CADL-3 scale contains 50 items assessing functional communication skills in seven areas of adults with neurogenic communication disorders. Participants receive a score of 0, 1, or 2 for each item. Higher scores reflect better communicative success.
Speech language function assessment	Change from baseline in ICF speech language function assessment. Aphasia adapted ICF speech language function assessment for self-evaluation of communication functions, participation, and activity. Minimum score -2, maximum score +2. Higher scores mean better outcome in quality of life.
Activities of daily living	Change from baseline in Barthel Index (BI) score

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Post stroke Depression assessment	Change from baseline in Hamilton Rating Scale for Depression (HRSD-24) score
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### Safety outcomes

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Muscle strength	Change from baseline in Medical Research Council grading system score
Spasticity	Change from baseline in the Modified Ashworth Scale (MAS) score
Range of motion	Change from baseline in range of motion of the main joints of the upper limbs score
Sensory function assessment	Change from baseline in the tactile sensory threshold and 2-point discrimination score

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### Brain plasticity evaluation

The explorative evaluations included the brain functional plasticity detection with functional Magnetic Resonance Imaging (MRI) and EEG evaluations. The resting-state, task-designed functional and structural MRI using a GE 3.0 T MRI scanner (MR750) will be collected at baseline, 3-week and 6-month follow-up. In task-designed MRI and EEG evaluations, picture naming task and semantic prediction task are used to assess patients' recovery and central plasticity mechanism of the recovery.

### Adverse events

The safety of patients will be monitored at each study visit point. Patients will receive a study information containing explicit details on whom to contact in case of an adverse event situation. Investigators will record all description of adverse events during each patient visit. In this clinical trial, severe adverse events (SAE) will be considered as death, life-threatening, or severe deterioration of health et al. Patients with SAEs will withdraw the clinical trial, as it is unsafe for them to continue the trial procedure. Once SAE occurs, investigators should take immediate treatment measures to ensure the safety of patients, and report to the IRB and relevant competent authorities within 24 hours of the occurrence of SAE.

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## 6 290 **Data collection and management**

8 291 Data are collected via the case report form (CRF) that was developed at the outset of the study. The  
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10 292 data administrator is responsible for reviewing and managing the entered data. After the data is  
11  
12 293 reviewed and the database is confirmed to be correct, it will be locked and submitted for statistical  
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14 294 analysis. The original data of the functional neuroimage will be burnt to disk, and the data without  
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16  
17 295 personal information of patients will be saved and analyzed.

## 20 296 **Analyses**

### 22 297 **Sample size**

24 298 This study intends to use the change of naming score from baseline to post-intervention as the  
25  
26 299 primary outcome. According to literature<sup>17 20</sup>, the naming score can be improved after intensive  
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29 300 speech therapy, and also can be verified after non-invasive brain stimulation therapy<sup>22 23</sup>. Combined  
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31 301 with our previous data, it is assumed that postoperative (NC7) + rehabilitation (iSLT) can improve  
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33 302 the naming ability with an average score of  $2.04 \pm 1.03$  points. While the iSLT alone group can  
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36 303 improve the naming ability with an average score of  $0.7 \pm 0.24$  points. With the power of 90% and  
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38 304 the 5% significant level(two-sided), the sample size of each group was 21. With loss to follow-up  
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40 305 rate is 15%, the total maximum sample size was 50 cases.

### 45 307 **Statistical analysis**

47 308 Analyses of primary endpoints will be performed in the full analysis set (FAS), which included all  
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49 309 randomly patients who received study treatment. Per-protocol set (PP) was defined as all patients  
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52 310 completing the study without major protocol deviation. Safety was evaluated in all randomly  
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54 311 assigned patients who received study treatment and analyzed using descriptive statistics.

56 312 Categorical data were described as frequency and percentage, and continuous data were described  
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59 313 by mean (standard deviation) or median (interquartile range). Between-group comparisons of  
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3 314 changes from baseline in primary and secondary outcome were performed using analysis of  
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5 315 covariance (ANCOVA). The baseline value and centre are covariates. Generalized estimating  
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8 316 equation (GEE) models were used to analysis the longitudinal data between groups. Subgroup  
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10 317 Analysis includes study centre, type of aphasia, etiology of aphasia, and severity of aphasia.  
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12 318 Sensitivity analysis was performed on missing data for the primary endpoint. All hypothesis tests  
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15 319 are two-sided, and values of  $P < 0.05$  is considered statistical significant.  
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## 19 20 321 **Ethics and dissemination**

21 322 The study has been approved by the Institutional Review Board of Huashan Hospital, Fudan  
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24 323 University (No. KY2021-592). All patients will write informed consent prior to entry to the study.  
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26 324 Patients may withdraw from the study at any time. Important protocol modifications will be  
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28 325 communicated to the relevant members of the research team. The procedure will be performed  
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30 326 following the principles described in the declaration of Helsinki.  
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## 35 328 **Patient and public involvement**

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37 329 We asked for the advice of patients of chronic aphasia after stroke in rehabilitation facilities that  
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40 330 meet the physical and emotional needs of the population. The doctors and therapists from the  
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42 331 rehabilitation facilities will provide support for recruitment. The results of the study will be  
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44 332 disseminated to the public on completion of the trial and the individual test results will be provided  
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47 333 to patients if request.  
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## 51 335 **DISCUSSION**

52 336 Due to the high morbidity and heavy diseases burden of stroke in China<sup>38</sup>, the effective treatments  
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54 337 of chronic aphasia after stroke are in urgent need. The current article describes the methodology of  
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56 338 a trial design for the effects of NC7 on symptom of language impairment in patients with chronic  
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339 aphasia after stroke. This study bears major importance because it could potentially provide  
340 evidence for the validity of a novel therapy strategy improving language function while diminishing  
341 the disfunctions after stroke.

342 This study focuses on the evaluation of postoperative language function. The language function can  
343 be assessed by methods such as naming tests, communication ability assessments, etc. Patients with  
344 aphasia who receive iSLT or non-invasive peripheral stimulation can exhibit improvements in  
345 naming ability<sup>32</sup> and social communication<sup>18</sup>, but the effect sizes were usually modest. In the  
346 previous study, we found that the naming ability of patients after CC7 was significantly improved,  
347 and many other researchers also used the number of correct spontaneous naming as the only  
348 BNT-related index for evaluating language function<sup>39 40</sup>. In this study, the primary outcome of  
349 evaluation index for language function is the BNT scale, and we will use WAB score, CADL  
350 Communication Scale, ADL Scale and Post-Stroke Depression Scale as secondary indicators from  
351 the aspects of language repetition, listening comprehension, communication ability, daily life and  
352 psychology. The ICF speech and language function assessment can detect the degree of changes in  
353 voice intonation, oral motor ability, articulation intelligibility, and oral expression of patients, to  
354 exclude the possible reduction of spasticity after neurotomy for the interference with study results.

355 The contralateral C7 nerve transfer (CC7) was first invented by Gu<sup>41-43</sup> to treat limb dysfunction  
356 after brachial plexus injury, the follow-up work<sup>44 45</sup> showed the neuroplastic changes between the  
357 hemispheres after surgery. Based on this theoretical perspective, Xu originally proposed the  
358 scientific viewpoint that "One hemisphere controls both limbs", and expanded the development of  
359 the "contralateral C7 nerve transfer" to "contralateral C7 to C7 cross nerve transfer" for treating  
360 central hemiplegia<sup>25 46 47</sup>. Our previous investigations have suggested the possible correlation  
361 between CC7 and the improvement of chronic aphasia, this effectiveness occurred in the early  
362 postoperative period, so the extent of the aphasia recovery after neurotomy of C7 nerve at  
363 intervertebral foramen caught our attention. In this study, we measured muscle strength, joint range

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3 364 of motion, upper limb MAS score and sensory assessment as safety indicators to evaluate the effect  
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6 365 of the NC7 on the right side. If the NC7 does improve language function with no physical  
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8 366 dysfunction, it will provide an entirely novel perspective for the treatment of chronic aphasia after  
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10 367 stroke. However, the mechanisms by which NC7 are thought to be effective in chronic aphasia but  
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12 368 not fully understood. We consider that this clinical phenomenon of language function improvement  
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15 369 is due to stimulate the neuroplasticity by NC7. This requires more objective functional imaging  
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17 370 evidence to confirm. Several recent publications have reviewed the mechanisms of aphasia recovery,  
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19 371 and in some cases the mechanisms of therapy<sup>48 49</sup> revealed by changes in task-related brain  
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22 372 activations or changes in functional connectivity within functional networks<sup>50 51</sup>. Here, we use fMRI  
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24 373 and EEG methods to observe around the naming ability and semantic prediction, to investigate the  
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26 374 neural and physiological states induced by changes in language function after NC7.  
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29 375 In conclusion, this is the first RCT to evaluate the surgical effect in patients with chronic aphasia  
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31 376 after stroke for whom no effective treatment is available. If found to be efficient, this strategy could  
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33 377 be regularly implemented, as it is easily applicable and low-cost. Moreover, larger trials could be  
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35 378 extended to other central nerve injury diseases to check for efficiency in language and other  
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38 379 functions. Once our hypothesis is confirmed, this trial will provide important evidence for  
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40 380 supporting neurotomy of C7 nerve at intervertebral foramen as a treatment approach for chronic  
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42 381 aphasia, which may provide a novel perspective on aphasia treatment and the interaction with  
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## 49 384 **Abbreviations**

51 385 RCT = randomized controlled trials; CC7 = contralateral C7 to C7 cross nerve transfer; NC7 =  
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54 386 neurotomy of C7 nerve at intervertebral foramen; iSLT = intensive speech and language therapy;  
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56 387 DRG=dorsal root ganglion; IRB = Institutional Review Board; BDAE= Boston Diagnostic Aphasia  
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58 388 Examination; BNT = Boston naming test; WAB = Western Aphasia Battery; CADL =  
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3 389 Communication Activities of Daily Living; ADL= Activity of Daily Living; ICF=International

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5 390 classification of Functioning, Disability and Health; HRSD= Hamilton Rating Scale for Depression

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7 391 , EEG = Electroencephalography; fMRI = functional magnetic resonance imaging; SAE = Severe

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9 392 Adverse Events.

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## 13 394 **Declarations**

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15 395 The authors declare that they have no competing interests.

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## 19 397 **Patient consent for publication**

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21 398 Not required.

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28

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30

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34

35 405 clinical medical research , Shanghai Medical College; Fudan University.

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44 409 University and all the participating institutions.

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## 48 411 **Contributors**

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50 412 WD-X is the principal investigator of this study and refined the protocol. TL and JT-F wrote the

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52 413 manuscript and contributed to the design of the study. MZ-L, the medical statistician for the study,

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3 414 contributed to the statistical design and ethical approval. WS-C contributed to brain plasticity  
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5  
6 415 evaluation design and guidance. YD-G participated in the concept and design of the study. RP-H,  
7  
8 416 XY-M, QJ-Q, YL, XE-C, LD have revised the protocol critically for multicentre intellectual  
9  
10 417 content. All authors read and approved the final manuscript.  
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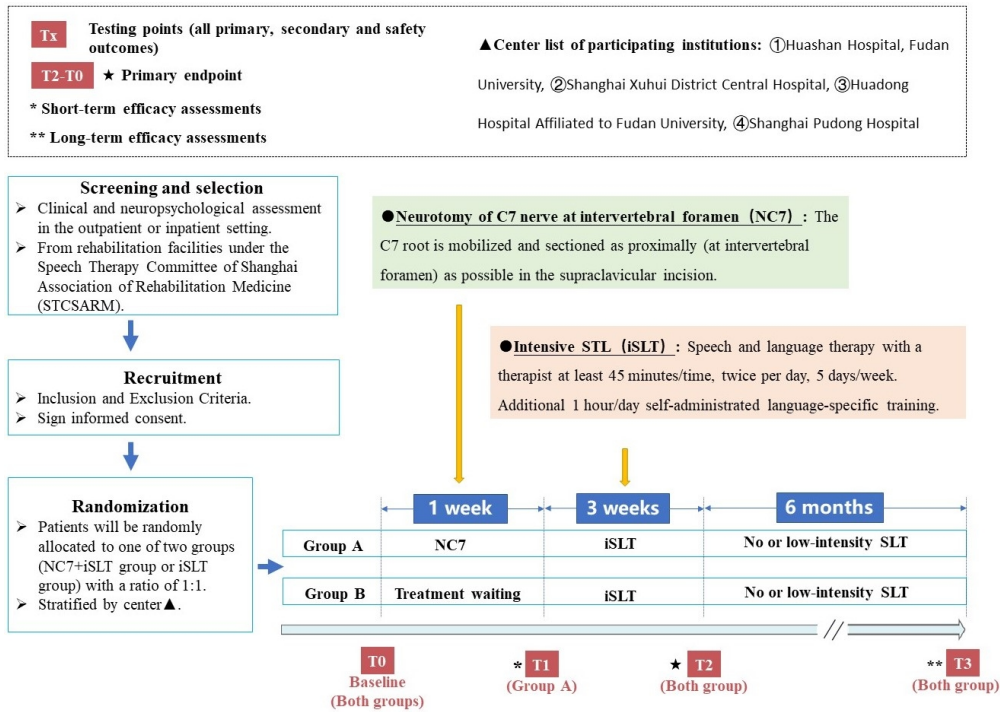
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## Figure caption

**Figure 1** - Trial design with details and the flow chart of patients through the trial.



Trial design with details and the flow chart of patients through the trial.

347x247mm (96 x 96 DPI)





STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
<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 _____
	2b	All items from the World Health Organization Trial Registration Data Set	_____ NA _____
Protocol version	3	Date and version identifier	_____ 1-2 _____
Funding	4	Sources and types of financial, material, and other support	_____ 18 _____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____ 1,18,19 _____
	5b	Name and contact information for the trial sponsor	_____ NA _____
	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	_____ NA _____
	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)	_____ 7, 9-14 _____

1 **Introduction**

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3 Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention \_\_\_\_\_ 4-6 \_\_\_\_\_

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6 6b Explanation for choice of comparators \_\_\_\_\_ 4-6 \_\_\_\_\_

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8 Objectives 7 Specific objectives or hypotheses \_\_\_\_\_ 6, 7 \_\_\_\_\_

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10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) \_\_\_\_\_ 7 \_\_\_\_\_

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14 **Methods: Participants, interventions, and outcomes**

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16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained \_\_\_\_\_ 9,10 \_\_\_\_\_

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19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) \_\_\_\_\_ 7,8 \_\_\_\_\_

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23 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered \_\_\_\_\_ 8,9 \_\_\_\_\_

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26 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) \_\_\_\_\_ 13-14 \_\_\_\_\_

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29 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) \_\_\_\_\_ NA \_\_\_\_\_

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32 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial \_\_\_\_\_ 8,9 \_\_\_\_\_

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34 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 \_\_\_\_\_ 11-13 \_\_\_\_\_

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40 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) \_\_\_\_\_ 11, 12 \_\_\_\_\_

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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including \_\_\_\_\_ 14 \_\_\_\_\_  
 2 clinical and statistical assumptions supporting any sample size calculations

3  
 4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size \_\_\_\_\_ 9-10 \_\_\_\_\_  
 5

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

7  
 8 Allocation:

9  
 10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any \_\_\_\_\_ 11 \_\_\_\_\_  
 11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction  
 12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants  
 13 or assign interventions  
 14  
 15

16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, \_\_\_\_\_ 11 \_\_\_\_\_  
 17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  
 18 mechanism  
 19

20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to \_\_\_\_\_ NA \_\_\_\_\_  
 21 interventions  
 22  
 23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome \_\_\_\_\_ 11 \_\_\_\_\_  
 25 assessors, data analysts), and how  
 26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's \_\_\_\_\_ NA \_\_\_\_\_  
 28 allocated intervention during the trial  
 29  
 30

31 **Methods: Data collection, management, and analysis**

32  
 33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related \_\_\_\_\_ 14 \_\_\_\_\_  
 34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of  
 35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.  
 36 Reference to where data collection forms can be found, if not in the protocol  
 37  
 38

39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be \_\_\_\_\_ NA \_\_\_\_\_  
 40 collected for participants who discontinue or deviate from intervention protocols  
 41  
 42

1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____ 14 _____
2				
3				
4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____ 14-15 _____
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____ 14-15 _____
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____ NA _____
11				
12				
13				
14	<b>Methods: Monitoring</b>			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____ NA _____
17				
18				
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21				
22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____ NA _____
23				
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____ 13-14 _____
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____ NA _____
29				
30				
31				
32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____ 15 _____
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____ NA _____
38				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ NA _____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ NA _____
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____ NA _____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 18 _____
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 14 _____
14				
15				
16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____ NA _____
17				
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____ 15 _____
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ NA _____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ NA _____
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__additional files__
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____ NA _____
35				
36				

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

## The effect and safety of C7 neurotomy at the intervertebral foramen in patients with chronic post-stroke aphasia: a multicentre, randomised, controlled study protocol

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3 1 **TITLE PAGE**  
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5 2 **The effect and safety of C7 neurotomy at the intervertebral foramen in patients with chronic**  
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7 3 **post-stroke aphasia: a multicentre, randomised, controlled study protocol**  
8

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40 33 **Keywords:** chronic post-stroke aphasia, C7 neurotomy (NC7) at the intervertebral foramen,  
41 34 intensive speech and language therapy (iSLT), neuroplasticity  
42 35

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3 40 **ABSTRACT**  
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- 5 41 • **Introduction:** Aphasia affects many stroke survivors, and effective treatments are urgently  
6 42 needed. The preliminary clinical findings implied an association between Contralateral C7 to C7  
7 43 Cross Nerve Transfer (CC7) and recovery of chronic aphasia. There is a lack of randomised  
8 44 control trial in support of the C7 neurotomy (NC7) efficacy. This study aims to explore the  
9 45 efficiency of NC7 at the intervertebral foramen in improving chronic post-stroke aphasia.  
10 46 • **Methods and analysis:** This study protocol reports a multicentre, randomised, controlled trial.  
11 47 A total of 50 patients with chronic post-stroke aphasia (onset time  $\geq$  12 months, aphasia quotient  
12 48 of Western Aphasia Battery [WAB] score  $\leq$  93.8) will be recruited. Participants will be  
13 49 randomly assigned to one of two groups (25 subjects each) to receive NC7 plus intensive speech  
14 50 and language therapy (iSLT) or iSLT alone programme. Since the study design does not allow  
15 51 participant blinding, the outcome assessor and the statistician will be blinded. The primary  
16 52 outcome is the change from baseline in BNT scores to post-intervention. The secondary  
17 53 outcomes include: the aphasia quotient of the WAB score, assessments on the International  
18 54 Classification of Functioning, Disability and Health, the Communication Activities of Daily  
19 55 Living scale, the Activities of Daily Living score, the Hamilton Depression Rating Scale and  
20 56 other surgical safety outcomes. The study also explores the functional imaging outcomes of  
21 57 naming tests and semantic violations that could reflect intervention-induced neuroplasticity.  
22 58 • **Ethics and dissemination:** This study was approved by the institutional review board of  
23 59 Huashan Hospital, Fudan University (No. KY2021-592) and by the institutional review boards  
24 60 of all the participating institutions. The findings will be disseminated through peer-reviewed  
25 61 publications and conference presentations.

26 62 **Trial registration:** ChiCTR2200057180  
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## ARTICLE SUMMARY

### Strengths and limitations of this study

- This is the first multicentre randomised controlled trial in neurosurgery aimed at improving language function in patients with chronic post-stroke aphasia.
- This study is helpful to answer the question, “How did speech evolve and what parts of the brain control it?”, which was listed in the 125 scientific questions in “Science” in 2021.
- A limitation of this study is not being double-blind but evaluator-blind, and the probability that the experimental group may get a minor placebo effect.

## INTRODUCTION

### Background and rationale

Aphasia refers to a collection of acquired receptive and expressive language deficits, which arise in many neurological diseases or post-trauma, but are most frequently observed after left hemisphere stroke<sup>1</sup>. More than 10 million new stroke cases are reported each year globally<sup>2</sup>, and at least one-third of these patients have symptoms of aphasia<sup>3</sup>. Aphasia is one of the most devastating symptoms in stroke survivors<sup>4 5</sup>, with substantial costs for individuals with stroke during the acute and chronic phases. Moreover, it is an independent predictor of subsequent functional dependence and death<sup>3 6</sup>.

The presence of aphasia predicts the care and rehabilitation needs<sup>7</sup> and the likelihood of failure to return to work<sup>8</sup>. Aphasia increases the burden on family and society.

Language is an indispensable part of cognitive function and affects patients' attention, comprehension and other functions<sup>9</sup>. Aphasia, language impairment after stroke or other neurological insults, is a common and often devastating condition affecting nearly every social activity and interaction. The language function of the patients will recover spontaneously to varying degrees<sup>10</sup>. The traditional view is that language function will reach the chronic phase 6-9 months after stroke, with few changes later<sup>11 12</sup>. During recovery, both the subtype and severity of aphasia change over time and patients may progress from sensory aphasia to conduction aphasia to naming aphasia to "recovered"<sup>13</sup>, although this "recovered" may also have a mild residual impairment that could be detected by a more sensitive assessment<sup>14</sup>. However, some forms of aphasia persist into

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2  
3 92 the chronic phase in half of the patients at least<sup>15</sup>.  
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5 93 Although most aphasia therapy studies have enrolled chronic patients, it seems likely that earlier  
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7 94 aphasia therapy is also effective, as it has achieved good results in improving aphasia after stroke<sup>16</sup>.  
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10 95 Common aphasia rehabilitation treatments include classic speech-language rehabilitation training,  
11  
12 96 as well as low-frequency electrical stimulation therapy, repetitive transcranial magnetic stimulation  
13  
14  
15 97 and transcranial direct current stimulation. Many clinical studies<sup>17 18</sup> have shown that speech and  
16  
17 98 language therapy (SLT) effectively improves communication, reading, writing, and language  
18  
19 99 expression in post-stroke aphasia patients, while the high-intensity and long-term mode may have  
20  
21 100 better effects<sup>19</sup>. A large-scale randomised control trial (RCT) study reported that<sup>18</sup>, 3 weeks of  
22  
23 101 intensive speech and language therapy (iSLT) showed treatment effects in patients with chronic  
24  
25 102 post-stroke aphasia, and significantly enhanced verbal communication among people aged 70 years  
26  
27 103 or younger. This beneficial outcome could be maintained for up to 6 months after treatment. Stahl<sup>20</sup>  
28  
29 104 further determined the optimal daily dosage and total duration of iSLT. The results showed no  
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31 105 added value from more than 2 hours of daily SLT within 4 weeks. In addition, non-invasive brain  
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33 106 stimulation therapy is widely used in the rehabilitation of various neurological diseases.  
34  
35 107 Transcranial direct current stimulation (tDCS) uses electrode pads to deliver a weak direct current  
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37 108 to specific brain regions of patients, which can affect the function of the cerebral cortex and help  
38  
39 109 improve the accuracy of noun naming in patients with aphasia<sup>21-23</sup>. However, there is still a lack of  
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41 110 enough data on the optimal sample size and a strict methodology. Low-frequency repetitive  
42  
43 111 transcranial magnetic stimulation (rTMS) is the regular and repeated application of a pulsed  
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45 112 magnetic field that briefly penetrates the skull to specific cortical regions and induces plastic  
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47 113 changes in the brain and language function in long-term post-stroke aphasia patients. However, its  
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49 114 efficacy is still controversial and needs further confirmation by large-scale clinical trials<sup>24</sup>.  
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56 115 We previously developed a surgical procedure for contralateral C7 transfer from the nonparalyzed  
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58 116 side to the paralyzed side (contralateral C7 to C7 cross nerve transfer [CC7]), after which patients  
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3 117 demonstrated improved motor function and reduced spasticity in the paralyzed arm over 12  
4  
5 118 months<sup>25</sup>. So far, more than 1,000 patients have undergone this surgery<sup>26</sup>. In addition to arm motor  
6  
7  
8 119 recovery, the improvement of language was frequently self-reported by patients and caregivers  
9  
10 120 during the follow-up, and it would occur very rapidly after CC7 treatment. A few days is far from  
11  
12 121 enough time for the transferred C7 nerve to regenerate<sup>27</sup>; therefore, we assumed that the rapid  
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14  
15 122 improvement of language function was mediated by the C7 neurotomy (NC7) on the paralyzed side  
16  
17 123 (right side) rather than nerve regeneration. During the CC7 operation<sup>28</sup>, to make the C7 nerve on the  
18  
19 124 paralyzed side can provide more nerve fibre length, we cut the C7 nerve root at the intervertebral  
20  
21  
22 125 foramen. Based on anatomical research, the anterior and posterior roots converge into spinal nerves  
23  
24 126 at the intervertebral foramen, and the posterior roots enlarge near the intervertebral foramen to form  
25  
26 127 ganglia, also known as dorsal root ganglion (DRG)<sup>29 30</sup>. The exact location of neurotomy is at the  
27  
28  
29 128 transitional junction of the C7 nerve root with DRG<sup>31</sup>. The human C7 nerve contains 80,000  
30  
31 129 fibers<sup>32</sup>, 94% of which are sensory fibres emitted by DRG<sup>33</sup>. Hence, the neurotomy of the C7 nerve  
32  
33 130 root at the junction with DRG can block the ascending sensory pathway from the affected limb to  
34  
35  
36 131 the brain. The mechanisms of language production are complex. The corresponding brain regions  
37  
38 132 and circuits involved in human language function are still unsolved mysteries, “How did speech  
39  
40 133 evolve and what parts of the brain control it?” listed in the 125 scientific questions by “Science”  
41  
42 134 journal (<https://www.science.org/content/resource/125-questions-exploration-and-discovery>, Page  
43  
44 135 34, Chapter Neuroscience, Q3). Based on the anatomy of brain functional areas, we hypothesized  
45  
46  
47 136 that, since the sensory-motor centre is adjacent to the language centre, if the sensory-motor centre  
48  
49 137 would be changed artificially by NC7 at the intervertebral foramen, then it is possible to induce the  
50  
51  
52 138 language centre and produce related functional changes. It may also be that NC7 leads to a change  
53  
54 139 in the interhemispheric balance, thus, affecting the functional neural circuits of language. We  
55  
56 140 designed this trial to evaluate the surgical effect of NC7 at the intervertebral foramen on underlying  
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59 141 neuroplasticity in patients with chronic post-stroke aphasia. Meanwhile, the iSLT is used as the  
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3 142 control method we will assess the effect of intensive intervention after 3 weeks and the maintenance  
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5  
6 143 of the effect after 6 months in both groups. Meanwhile, we use neuroimaging methods to provide  
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8 144 objective data as evidence to support our hypothesis.  
9

10 145

## 11 146 **Aims of the study**

12 147 The study aims to evaluate the therapeutic efficacy of the NC7 at the intervertebral foramen on  
13  
14 148 language impairment in patients with chronic post-stroke aphasia. The current paper describes the  
15  
16 149 design of this study.  
17

18 150 Our specific objectives are: (1) to evaluate the comparative effectiveness of different interventions,  
19  
20 151 NC7 plus iSLT (3 weeks) and iSLT (3 weeks) alone, and the further validation of the safety and  
21  
22 152 long-term effectiveness (6 months) of the NC7 surgical programme. (2) To evaluate the motor and  
23  
24 153 sensorimotor function of the paralyzed arm and clarify the correlation between motor function and  
25  
26 154 language function changes postoperatively. (3) To confirm the central mechanism of NC7 at the  
27  
28 155 intervertebral foramen and access the underlying neuroplasticity via functional neuroimaging  
29  
30 156 measurements.  
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## 39 158 **METHODS AND ANALYSIS**

### 40 159 **Trial design**

41  
42 160 This study is a multicentre, randomised controlled trial with two parallel groups and a 6-month  
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44 161 follow-up. Based on language and motor function analysis, the protocol compares patients with  
45  
46 162 chronic aphasia treated with the NC7 at the intervertebral foramen and iSLT (Group A), with a  
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48 163 control group participating in iSLT alone (Group B). The participants will be randomly allocated to  
49  
50 164 one of the two groups (NC7+iSLT group or iSLT alone group) with a ratio of 1:1. The study is  
51  
52 165 conducted in collaboration with the Speech Therapy Committee of the Shanghai Association of  
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54 166 Rehabilitation Medicine, and the participants will be recruited from rehabilitation facilities of this  
55  
56 167 organization. Patients will receive an indication for outpatient rehabilitation treatment at any of the  
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3 168 four centres (Supplemental Table 1), based on the eligibility criteria listed below. The potentially  
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6 169 eligible patients will be invited to participate in the study via a text message after signing an  
7  
8 170 informed consent.

9  
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## 12 172 **Eligibility criteria**

14 173 Inclusion criteria:

- 16 174 1) Aphasia for over 12 months after a single onset of infarction or haemorrhage of the left  
18  
19 175 hemisphere, confirmed by magnetic resonance imaging;
- 21 176 2) Age: 40-65 years, sex: male or female, right-handed, native Chinese speaker;
- 23 177 3) Aphasia quotient below 93.8 points assessed by Western Aphasia Battery;
- 25  
26 178 4) Severity score assessed by BDAE test: level 1 and above;
- 27  
28 179 5) Good compliance and ability to cooperate with language rehabilitation training;
- 29  
30 180 6) Ability to fully understand and agree with the doctor's treatment plan and sign the informed  
31  
32 181 consent.

34  
35 182 Criteria 3 and 4 need to be confirmed by two attending specialists' diagnostic evaluation.

37 183 Exclusion criteria:

- 39 184 1) Surgical contraindications (any reason) determined by a qualified anaesthesiologist or clinician;
- 41  
42 185 2) A history of aphasia before the last onset of the stroke;
- 43  
44 186 3) Serious, untreated mental illness;
- 45  
46 187 4) Aphasia due to neurodegenerative diseases or traumatic brain injury;
- 47  
48  
49 188 5) Presenting contraindications for EEG and MRI evaluation;
- 50  
51 189 6) Unable to complete the assessments and rehabilitation required by the study design;
- 52  
53 190 7) Severe motor speech disorder and hearing impairment;
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55  
56 191 8) Having received intensive post-stroke rehabilitation therapy 4 weeks before recruitment.

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## 60 193 **Interventions**

### 194 **NC7 at the intervertebral foramen**

195 Make a 6-cm long longitudinal incision along the medial border of the sternocleidomastoid muscle  
196 on the right side after the cervical plexus under anaesthesia/general anaesthesia (depending on the  
197 patient's preference and the anaesthesiologist's risk assessment). Carefully separate the structure  
198 layer by layer and identify the brachial plexus by marking the C7 nerve with a vessel loop. Next,  
199 the C7 root is mobilized and sectioned as proximally (at the intervertebral foramen) as possible.  
200 Considering that some patients have limb hemiplegia, CC7 surgery may be required to improve  
201 limb function at the end of this trial. Therefore, we fix the severed C7 root to the fascia at the  
202 junction of the scapulothyoid and sternocleidomastoid muscles with silk thread, making it easier to  
203 find and anastomose with the contralateral C7 root during the later CC7<sup>28</sup> surgical intervention.

### 205 **iSLT Rehabilitation**

206 Considering previous studies' results, we formulated a 3-week iSLT plan. Speech and language  
207 therapy with a therapist for at least 45 minutes, twice daily, 5 days/week. Additional 1 hour/day  
208 self-administrated language-specific training. Patients receive rehabilitation treatment at different  
209 centres, where qualified rehabilitation therapists perform the therapy.

### 211 **Study setting**

212 This study started on July 2022, participants will be recruited between July 2022 and July 2023.  
213 Study completion is expected to be July 2024. A total of 50 patients diagnosed with chronic  
214 aphasia and hemiplegia after stroke will be recruited. Patients in the research institutions will  
215 receive in-hospital treatment for 3 to 4 weeks, with follow-up assessment at 6 months (Figure 1).  
216 Patients will be selected based on the study eligibility criteria on their first visit. Then, eligible  
217 patients will be randomly assigned to one of the two groups in different centres. Patients of Group  
218 A will receive NC7 immediately after assignment and receive a short-term efficacy assessment 3

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3 219 days later. The total perioperative period is one week. Meanwhile, patients of Group B are awaiting  
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6 220 the therapy programme, and also receive a short-term efficacy assessment after 3 days later. The  
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8 221 iSLT and upper extremity motor rehabilitation programme are provided for patients in both groups.  
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10 222 After a 3-week inpatient intervention, all the patients receive primary endpoint assessments, and then  
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12 223 they continue to receive conventional low-intensity SLT at home or in other centres. For arm motor  
13  
14 224 function follow-up, patients are guided to perform the rehabilitation programme consistently while  
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16  
17 225 a therapist or caregiver records the intensity and duration of the therapy. Six months later, all  
18  
19 226 patients will receive an interim evaluation by a trained therapist from an independent team on their  
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21  
22 227 second visit. Afterwards, the NC7 and postoperative rehabilitation programme, which is consistent  
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24 228 with Group A, are performed in patients of Group B. Likewise, these patients will receive a short-  
25  
26 229 term and long-term follow-up for efficacy assessment. The schedule of enrolment, interventions and  
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28  
29 230 assessments are presented in Table 1.

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### 32 232 **Participant timeline**

34 233 The schedule is presented in Table 1.

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37 235 **Table 1. Timeline schedule of enrolment, interventions and assessments.**

38 NC7+iSLT (Group A: experimental group)					
39 TIMEPOINT	40 Visit 1 (Eligibility screen)	41 Visit 2 (Baseline)	42 Visit 3 (3d+1d post- NC7)	43 Visit 4 (3w±3d post iSLT onset)	44 Visit 5 (24w±7d post iSLT end)
45 <b>Informed consent</b>	46 √				
47 <b>Inclusion and Exclusion Criteria</b>	48 √				
49 <b>Demographic variables</b> Age, sex, education, etc.	50 √				
51 <b>General physical examination</b>	52 √				
53 <b>Primary outcome</b>		54 √	55 √	56 √	57 √
58 <b>Secondary outcomes</b>		59 √	60 √	√	√

<b>Safety outcomes</b>		√	√	√	√
<b>Brain plasticity evaluation</b>		√		√	√
<b>Endpoint</b>			√	√	√
<b>Adverse events assessment</b>			√	√	√
<b>iSLT alone (Group B: control group)</b>					
<b>TIMEPOINT</b>	<b>Visit 1 (Eligibility screen)</b>	<b>Visit 2 (Baseline)</b>	<b>Visit 3 (3d+1d post-treatment waiting onset)</b>	<b>Visit 4 (3w±3d post iSLT onset)</b>	<b>Visit 5 (24w±7d post iSLT end)</b>
<b>Informed consent</b>	√				
<b>Inclusion and Exclusion Criteria</b>	√				
<b>Demographic variables</b> Age, sex, education, etc.	√				
<b>General physical examination</b>	√				
<b>Primary outcome</b>		√	√	√	√
<b>Secondary outcomes</b>		√	√	√	√
<b>Safety outcomes</b>		√	√	√	√
<b>Brain plasticity evaluation</b>		√		√	√
<b>Endpoint</b>			√	√	√
<b>Adverse events assessment</b>			√	√	√

(d) day, (w) week, (m) month.

(NC7) C7 neurotomy at the intervertebral foramen, (iSLT) intensive speech and language therapy.

## Randomization and blinding

This study's stratified block randomization process is done by using an interactive web response system (IWRS), and the stratified factor is the centre (Huashan Hospital, Fudan University; Shanghai Pudong Hospital; Huadong Hospital affiliated to Fudan University, Shanghai Xuhui Central Hospital). The blinding method of this clinical trial is applied in the outcome evaluation stage. During the onsite evaluation process, patients will be required to wear a cervical collar to



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2  
3 246 cover the neck (wound site of patients in the experimental group), which will be videotaped. An  
4  
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6 247 independent team of trained therapists will conduct the video recording and performance scoring  
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8 248 process.

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## 11 **Outcomes measures**

12 250  
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14 251 The primary outcome is the change in total score on the Boston naming test (BNT) scale of Group  
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16 252 A and B from baseline (T0) to post-intervention, week 4(T2). BNT is a classic measurement tool  
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18  
19 253 for evaluating language function; the international version is BNT-60. The BNT scale shows a high  
20  
21 254 concurrent validity with other standard naming ability assessment tools, and it is particularly  
22  
23 255 suitable in the post-acute/chronic phase after stroke aphasia. In this study, we chose the validated  
24  
25  
26 256 Chinese version of BNT<sup>34 35</sup>.

27  
28 257 The secondary outcomes include aphasia quotient, daily communication (Communication Activities  
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30 258 of Daily Living–Third Edition [CADL-3]), activities of daily living (Barthel Index), speech  
31  
32  
33 259 language function assessment (ICF<sup>36</sup> speech language function assessment), post-stroke depression  
34  
35 260 assessment (Hamilton Rating Scale for Depression, HRSD) and safety outcomes in different  
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37 261 groups. Assessments performed to collect data for the primary, secondary, and safety outcomes are  
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39 262 listed in Table 2.

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44 264 **Table 2. Assessments performed to collect data for the primary, secondary, and safety**  
45 265 **outcomes**

46 <b>Variable</b>	47 <b>Measure</b>
48 <b>Primary outcome</b>	
49 Naming ability	50 Change from baseline in Boston Naming Test (BNT) score. 51 The BNT scale is a performance-based measure commonly 52 used to assess the visual confrontation naming ability among 53 adults with aphasia. Participants are shown pictures of 54 common objects and asked to name each stimulus item 55 within 20 seconds: minimum score of 0, maximum score of 56 60. Higher scores mean better outcomes in naming ability.
58 <b>Secondary outcome</b>	
59 Aphasia quotient	60 Change from baseline in WAB score

	<p>The WAB scale is a weighted average of all subtest scores relating to spoken language. It is a sum of all subtest scores from the first four parts of the WAB (spontaneous speech, Auditory verbal comprehension, Repetition, Naming and word finding), recording the total average score and standard deviation. The total range is 0-100 (higher scores indicating better performance).</p>
Daily communication	<p>Change from baseline in the Communication Activities of Daily Living–Third Edition (CADL-3)</p> <p>The CADL-3 scale contains 50 items assessing functional communication skills in seven areas of adults with neurogenic communication disorders. Participants receive a score of 0, 1, or 2 for each item. Higher scores reflect better communicative success.</p>
Speech language function assessment	<p>Change from baseline in ICF speech language function assessment.</p> <p>Aphasia-adapted ICF speech language function assessment for self-evaluation of communication functions, participation, and activity. Minimum score -2, maximum score +2. Higher scores mean better outcome in quality of life.</p>
Activities of daily living	Change from baseline in Barthel Index (BI) score
Post-stroke Depression assessment	Change from baseline in Hamilton Rating Scale for Depression (HRSD-24) score
<b>Safety outcomes</b>	
Muscle strength	Change from baseline in Medical Research Council grading system score
Spasticity	Change from baseline in the Modified Ashworth Scale (MAS) score
Range of motion	Change from baseline in range of motion of the main joints of the upper limbs score
Sensory function assessment	Change from baseline in the tactile sensory threshold and 2-point discrimination score

### 267 **Brain plasticity evaluation**

268 The explorative evaluations included brain functional plasticity detection with functional magnetic  
269 resonance imaging (MRI) and EEG evaluations. The resting-state, task-designed functional and  
270 structural MRI using a GE 3.0 T MRI scanner (MR750) will be collected at baseline, 3-week and 6-  
271 month follow-up. In task-designed MRI and EEG evaluations, picture naming tasks and semantic  
272 prediction tasks are used to assess patients' recovery and the central plasticity mechanism of the  
273 recovery.

### 275 **Adverse events**

276 The safety of patients will be monitored at each study visit point. Patients will receive study  
277 information containing explicit details on whom to contact in case of an adverse event. Investigators  
278 will record all descriptions of adverse events during each patient visit. In this clinical trial, death,  
279 life-threatening, severe deterioration of health, etc., will be considered severe adverse events (SAE).  
280 Patients with SAEs will withdraw from the clinical trial, as it would be unsafe to continue the trial  
281 procedure. Once SAE occurs, investigators should take immediate treatment measures to ensure the  
282 safety of patients and report to the institutional review board and relevant competent authorities  
283 within 24 hours of the occurrence of SAE.

### 285 **Data collection and management**

286 Data are collected via a case report form developed at the outset of the study. The data  
287 administrator is responsible for reviewing and managing the entered data. After the data is checked  
288 and the database is confirmed correct, it will be locked and submitted for statistical analysis. The  
289 original data of the functional neuroimage will be presented as a disk, and the data without patients'  
290 personal information will be saved and analysed.

### 291 **Analyses**

## 292 **Sample size**

293 This study intends to use the change of the naming score from baseline to post-intervention as the  
294 primary outcome. According to the literature<sup>17 20</sup>, the naming score can be improved after intensive  
295 speech therapy and verified after non-invasive brain stimulation therapy<sup>22 23</sup>. Combined with our  
296 previous data, it is assumed that postoperative (NC7) followed by rehabilitation (iSLT) can improve  
297 the naming ability with an average score of  $2.04 \pm 1.03$  points. In comparison, the iSLT-alone  
298 group can improve the naming ability with an average score of  $0.7 \pm 0.24$  points. With the power of  
299 90% and the 5% significant level (two-sided), the sample size of each group was 21. With a loss to  
300 follow-up rate of 15%, the total maximum sample size was 50 cases.

## 302 **Statistical analysis**

303 Analyses of primary endpoints will be performed in the full analysis set, which includes all random  
304 patients who received study treatment. Per-protocol set is defined as all patients completing the  
305 study without major protocol deviation. Safety is evaluated in all randomly assigned patients  
306 receiving study treatment and analysed using descriptive statistics.

307 Categorical data are presented as frequency and percentage, and continuous data are described by  
308 mean (standard deviation) or median (interquartile range). Between-group comparisons of changes  
309 from baseline in primary and secondary outcomes are performed using analysis of covariance. The  
310 baseline value and centre are covariates. Generalized estimating equation models are used to  
311 analyse the longitudinal data between groups. Subgroup analysis includes study centre, type of  
312 aphasia, aetiology of aphasia, and severity of aphasia. Sensitivity analysis is performed on missing  
313 data for the primary endpoint. All hypothesis tests are two-sided, and values of  $P < 0.05$  is  
314 considered statistically significant.

## 316 **ETHICS AND DISSEMINATION**

317 The study has been approved by the Institutional Review Board of Huashan Hospital, Fudan

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318 University (No. KY2021-592). All patients will sign an informed consent prior to entry into the  
319 study. Patients may withdraw from the study at any time. Important protocol modifications will be  
320 communicated to the relevant members of the research team. The procedure will be performed  
321 following the principles described in the declaration of Helsinki. Ethical approval for this trial was  
322 granted by the institutional review board of Huashan Hospital, Fudan University, and by the  
323 institutional review boards of all participating institutions (Supplemental Table 1).

### 325 **Patient and public involvement**

326 We asked for the advice of patients with chronic aphasia after stroke in rehabilitation facilities that  
327 meet the physical and emotional needs of the population. The doctors and therapists from the  
328 rehabilitation facilities will provide support for the recruitment. The study results will be  
329 disseminated to the public upon completion of the trial and the individual test results will be  
330 provided to patients upon request.

### 332 **DISCUSSION**

333 Due to the high morbidity and heavy disease burden of stroke in China<sup>37</sup>, there is an urgent need for  
334 effective treatments of chronic post-stroke aphasia. The current manuscript describes the  
335 methodology of a trial design for the effects of NC7 on language impairment symptoms in patients  
336 with chronic post-stroke aphasia. This study bears major importance because it could provide  
337 evidence for the validity of a novel therapeutic strategy for improving language function while  
338 diminishing dysfunctions after stroke.

339 This study focuses on the evaluation of postoperative language function. The language function can  
340 be assessed by naming tests, communication ability assessments, etc. Patients with aphasia who  
341 receive iSLT or non-invasive peripheral stimulation can exhibit improvements in naming ability<sup>38</sup>  
342 and social communication<sup>18</sup>, but the effect sizes were usually modest. In the previous study, we

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3 343 found that the naming ability of patients after CC7 was significantly improved, and many other  
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6 344 researchers also used the correct spontaneous naming scores as the only BNT-related index for  
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8 345 evaluating language function<sup>39 40</sup>. In this study, we use the BNT scale as an evaluation index for  
9  
10 346 language function for the primary outcome, and we will use WAB, CADL Communication Scale,  
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12 347 ADL Scale, and Post-Stroke Depression Scale scores as secondary indicators in the aspects of  
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15 348 language repetition, listening comprehension, communication ability, daily life, and psychology.  
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17 349 The ICF speech and language function assessment can detect the degree of changes in voice  
18  
19 350 intonation, oral motor ability, articulation intelligibility, and oral expression of patients to exclude  
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21  
22 351 the possible reduction of spasticity after neurotomy for the interference with study results.  
23  
24 352 The CC7 was first invented by Gu<sup>41-43</sup> to treat limb dysfunction after brachial plexus injury, and the  
25  
26 353 follow-up work<sup>44 45</sup> showed neuroplastic changes between the hemispheres after surgery. Based on  
27  
28  
29 354 this theoretical perspective, Xu originally proposed the scientific viewpoint that "One hemisphere  
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31 355 controls both limbs" and expanded the development of the "contralateral C7 nerve transfer" to  
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33 356 "contralateral C7 to C7 cross nerve transfer" for treating central hemiplegia<sup>25 46 47</sup>. Our previous  
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36 357 investigations suggested the possible correlation between CC7 and the improvement of chronic  
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38 358 aphasia, an effect occurring in the early postoperative period; thus, the possibility of aphasia  
39  
40 359 recovery after NC7 at the intervertebral foramen caught our attention. In this study, we measured  
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42 360 muscle strength, joint range of motion, upper limb MAS score and sensory assessment as safety  
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45 361 indicators to evaluate the effect of the NC7 on the right side. If the NC7 does improve language  
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47 362 function with no physical dysfunction, it will provide an entirely novel perspective for the treatment  
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49 363 of chronic post-stroke aphasia. However, the mechanisms involved in NC7 effectiveness in chronic  
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52 364 aphasia are not fully understood. We consider that this clinical phenomenon of language function  
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54 365 improvement is related to NC7 stimulating neuroplasticity. This requires more objective functional  
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56 366 imaging evidence to confirm. Several recent publications review the mechanisms of aphasia  
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58 367 recovery. In some cases, the therapy mechanisms<sup>48 49</sup> are evidenced by changes in task-related  
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3 368 brain activations or changes in functional connectivity within functional networks<sup>50 51</sup>. Here, we use  
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5 369 fMRI and EEG methods in relation to the naming ability and semantic prediction to investigate the  
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8 370 neural and physiological states induced by changes in the language function after NC7.  
9  
10 371 In conclusion, this is the first RCT to evaluate the surgical effect in patients with chronic post-  
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12 372 stroke aphasia for whom there is no effective treatment available. If found to be efficient, this  
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15 373 strategy could be regularly implemented due to its easy application and low cost. Moreover, larger  
16  
17 374 trials could be extended to other diseases with a central nerve injury to assess for this strategy's  
18  
19 375 efficiency on language and other functions. Once our hypothesis is confirmed, this trial will provide  
20  
21  
22 376 important evidence for supporting NC7 at the intervertebral foramen as a novel treatment approach  
23  
24 377 for chronic aphasia. A limitation of this study is that it is not double-blind but evaluator-blind, and  
25  
26 378 the experimental group may involve a minor placebo effect. To offset the short-term placebo effect  
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29 379 after surgery, we conducted a secondary endpoint assessment at 6 months. At that time, the patient's  
30  
31 380 placebo effect due to invasive interventions will be greatly reduced.  
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### 36 382 **Abbreviations list**

37  
38 383 RCT = randomised controlled trials; CC7 = contralateral C7 to C7 cross nerve transfer; NC7 = C7  
39  
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41 384 neurotomy; iSLT = intensive speech and language therapy; DRG=dorsal root ganglion; BDAE=  
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43 385 Boston Diagnostic Aphasia Examination; BNT = Boston naming test; WAB = Western Aphasia  
44  
45 386 Battery; CADL = Communication Activities of Daily Living; ADL= Activity of Daily Living;  
46  
47  
48 387 ICF=International classification of Functioning, Disability and Health; HRSD= Hamilton Rating  
49  
50 388 Scale for Depression, EEG = Electroencephalography; fMRI = functional magnetic resonance  
51  
52 389 imaging; SAE = Severe Adverse Events.  
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### 57 391 **Competing Interests**

58  
59 392 None declared.  
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## 5 394 **Patient consent for publication**

7  
8 395 Not required.  
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10 396  
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32  
33 406 University and all the participating institutions.  
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## 38 408 **Contributors**

39 409 WX is the principal investigator of this study and refined the protocol. TL and JF wrote the  
40  
41 manuscript and contributed to the design of the study. ML, the medical statistician for the study,  
42 410  
43 contributed to the statistical design and ethical approval. WC contributed to brain plasticity  
44 411  
45 evaluation design and guidance. YG participated in the concept and design of the study. RH, XM,  
46 412  
47 WQ, YZ, XC, LD have revised the protocol critically for multicentre intellectual content. All  
48 413  
49 414 authors read and approved the final manuscript.  
50  
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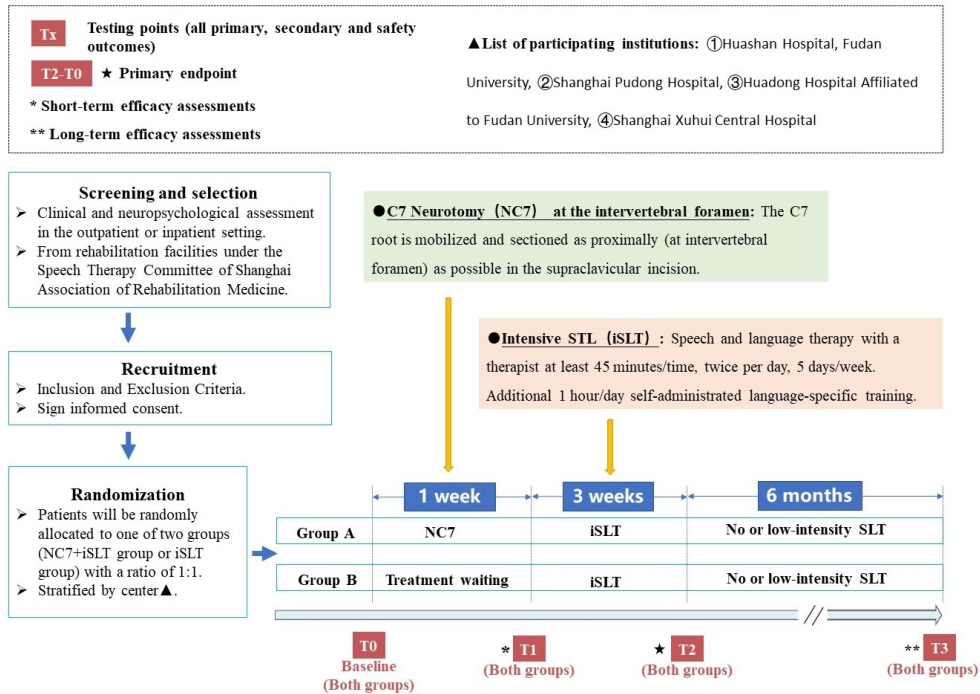
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## Figure caption

**Figure 1.** Trial design in detail and patients flow chart.



Trial design in detail and patients flow chart.

355x248mm (96 x 96 DPI)

**Supplemental Table 1. List of all participating institutions and institutional review boards in this trial**

<b>Major research institution</b>	<b>Name of institutional review board</b>
Huashan Hospital, Fudan University	Institutional Review Board of Huashan Hospital Affiliated to Fudan University
<b>Sub-centre research institution</b>	<b>Name of institutional review board</b>
Shanghai Pudong Hospital	Academic Ethics Committee of Shanghai Pudong Hospital
Huadong Hospital Affiliated to Fudan University	Ethics Committee of Huadong Hospital Affiliated to Fudan University
Shanghai Xuhui Central Hospital	Shanghai Xuhui Central Hospital Ethics Committee





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

Section/item	Item No	Description	Addressed on page number
<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 _____
	2b	All items from the World Health Organization Trial Registration Data Set	_____ NA _____
Protocol version	3	Date and version identifier	_____ 1-2 _____
Funding	4	Sources and types of financial, material, and other support	_____ 18 _____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____ 1,18,19 _____
	5b	Name and contact information for the trial sponsor	_____ NA _____
	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	_____ NA _____
	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)	_____ 6-7, 13-15 _____

1	<b>Introduction</b>			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	_____ 3-6 _____
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	_____ 3-6 _____
7				
8	Objectives	7	Specific objectives or hypotheses	_____ 6, 7 _____
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____ 6,7 _____
12				
13				
14	<b>Methods: Participants, interventions, and outcomes</b>			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	_____ 8,9 _____
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	_____ 7,8 _____
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	_____ 8 _____
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	_____ 13-14 _____
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	_____ NA _____
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____ 8,9 _____
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	_____ 11-13 _____
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	_____ 11, 12 _____
39			participants. A schematic diagram is highly recommended (see Figure)	
40				
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____14_____
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____8,9_____
5				

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

#### 7 Allocation:

8				
9				
10	Sequence	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____10,11_____
11	generation			
12				
13				
14				
15				
16	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____10,11_____
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____NA_____
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____10,11_____
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA_____
28				
29				
30				

### 31 **Methods: Data collection, management, and analysis**

32				
33	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____13,14_____
34	methods			
35				
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38				
39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____NA_____
40				
41				
42				

1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____ 13,14 _____
2				
3				
4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____ 14,15 _____
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____ 14,15 _____
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____ NA _____
11				
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13				

14 **Methods: Monitoring**

15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____ NA _____
17				
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____ NA _____
23				
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____ 13 _____
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____ NA _____
29				
30				
31				

32 **Ethics and dissemination**

33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____ 15 _____
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____ NA _____
38				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____NA_____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____NA_____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____18_____
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____13,14_____
14				
15				
16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____NA_____
17				
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____15_____
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____NA_____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____NA_____
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Supplemental Material__
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____NA_____
35				
36				

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

# BMJ Open

## The effect and safety of C7 neurotomy at the intervertebral foramen in patients with chronic post-stroke aphasia: a multicentre, randomised, controlled study protocol

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Manuscript ID	bmjopen-2022-065173.R2
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<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Neurology, Surgery
Keywords:	Stroke < NEUROLOGY, Neurosurgery < SURGERY, Clinical trials < THERAPEUTICS

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Manuscripts

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5 2 **The effect and safety of C7 neurotomy at the intervertebral foramen in patients with chronic**  
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7 3 **post-stroke aphasia: a multicentre, randomised, controlled study protocol**  
8

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45 33 **Keywords:** chronic post-stroke aphasia, C7 neurotomy (NC7) at the intervertebral foramen,  
46 34 intensive speech and language therapy (iSLT), neuroplasticity  
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49 36 **Word count: 4396**  
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## ABSTRACT

- **Introduction:** Aphasia affects many stroke survivors, and effective treatments are urgently needed. The preliminary clinical findings implied an association between Contralateral C7 to C7 Cross Nerve Transfer (CC7) and recovery of chronic aphasia. There is a lack of randomised controlled trials in support of the C7 neurotomy (NC7) efficacy. This study aims to explore the efficiency of NC7 at the intervertebral foramen in improving chronic post-stroke aphasia.
- **Methods and analysis:** This study protocol reports a multicentre, randomised, controlled trial. A total of 50 patients with chronic post-stroke aphasia (onset time  $\geq$  12 months, aphasia quotient of Western Aphasia Battery [WAB] score  $\leq$  93.8) will be recruited. Participants will be randomly assigned to one of two groups (25 subjects each) to receive NC7 plus intensive speech and language therapy (iSLT) or iSLT alone programme. Since the study design does not allow participant blinding, the outcome assessor and the statistician will be blinded. The primary outcome is the change from baseline in BNT scores to post-intervention. The secondary outcomes include: the aphasia quotient of the WAB score, assessments on the International Classification of Functioning, Disability and Health, the Communication Activities of Daily Living scale, the Activities of Daily Living score, the Hamilton Depression Rating Scale and other surgical safety outcomes. The study also explores the functional imaging outcomes of naming tests and semantic violations that could reflect intervention-induced neuroplasticity.
- **Ethics and dissemination:** This study was approved by the institutional review board of Huashan Hospital, Fudan University (No. KY2021-592) and by the institutional review boards of all the participating institutions. The findings will be disseminated through peer-reviewed publications and conference presentations.

**Trial registration:** ChiCTR2200057180

## ARTICLE SUMMARY

### Strengths and limitations of this study

- This is the first multicentre randomised controlled trial in neurosurgery aimed at improving language function in patients with chronic post-stroke aphasia.
- This study will explore the possibility of a new strategy based on peripheral neurosurgery and traditional rehabilitation treatment to improve multiple dysfunction after central nervous system injury.
- A limitation of this study is not being double-blind but evaluator-blind, and the probability that the experimental group may get a minor placebo effect.

## INTRODUCTION

### Background and rationale

Aphasia refers to a collection of acquired receptive and expressive language deficits, which arise in many neurological diseases or post-trauma, but are most frequently observed after left hemisphere stroke<sup>1</sup>. More than 10 million new stroke cases are reported each year globally<sup>2</sup>, and at least one-third of these patients have symptoms of aphasia<sup>3</sup>. Aphasia is one of the most devastating symptoms in stroke survivors<sup>4 5</sup>, with substantial costs for individuals with stroke during the acute and chronic phases. Moreover, it is an independent predictor of subsequent functional dependence and death<sup>3 6</sup>. The presence of aphasia predicts the care and rehabilitation needs<sup>7</sup> and the likelihood of failure to return to work<sup>8</sup>. Aphasia increases the burden on family and society.

Language is an indispensable part of cognitive function and affects patients' attention, comprehension and other functions<sup>9</sup>. Aphasia, language impairment after stroke or other neurological insults, is a common and often devastating condition affecting nearly every social activity and interaction. The language function of the patients will recover spontaneously to varying degrees<sup>10</sup>. The traditional view is that language function will reach the chronic phase 6-9 months after stroke, with few changes later<sup>11 12</sup>. During recovery, both the subtype and severity of aphasia change over time and patients may progress from sensory aphasia to conduction aphasia to naming aphasia to "recovered"<sup>13</sup>, although this "recovered" may also have a mild residual impairment that could be detected by a more sensitive assessment<sup>14</sup>. However, some forms of aphasia persist into

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2  
3 92 the chronic phase in half of the patients at least<sup>15</sup>.  
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5 93 Although most aphasia therapy studies have enrolled chronic patients, it seems likely that earlier  
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7 94 aphasia therapy is also effective, as it has achieved good results in improving aphasia after stroke<sup>16</sup>.  
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10 95 Common aphasia rehabilitation treatments include classic speech-language rehabilitation training,  
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12 96 as well as low-frequency electrical stimulation therapy, repetitive transcranial magnetic stimulation  
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14 97 and transcranial direct current stimulation. Many clinical studies<sup>17 18</sup> have shown that speech and  
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16 98 language therapy (SLT) effectively improves communication, reading, writing, and language  
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18 99 expression in post-stroke aphasia patients, while the high-intensity and long-term mode may have  
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20 100 better effects<sup>19</sup>. A large-scale randomised control trial (RCT) study reported that<sup>18</sup>, 3 weeks of  
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22 101 intensive speech and language therapy (iSLT) showed treatment effects in patients with chronic  
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24 102 post-stroke aphasia, and significantly enhanced verbal communication among people aged 70 years  
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26 103 or younger. This beneficial outcome could be maintained for up to 6 months after treatment. Stahl<sup>20</sup>  
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28 104 further determined the optimal daily dosage and total duration of iSLT. The results showed no  
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30 105 added value from more than 2 hours of daily SLT within 4 weeks. In addition, non-invasive brain  
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32 106 stimulation therapy is widely used in the rehabilitation of various neurological diseases.  
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34 107 Transcranial direct current stimulation (tDCS) uses electrode pads to deliver a weak direct current  
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36 108 to specific brain regions of patients, which can affect the function of the cerebral cortex and help  
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38 109 improve the accuracy of noun naming in patients with aphasia<sup>21-23</sup>. However, there is still a lack of  
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40 110 enough data on the optimal sample size and a strict methodology. Low-frequency repetitive  
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42 111 transcranial magnetic stimulation (rTMS) is the regular and repeated application of a pulsed  
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44 112 magnetic field that briefly penetrates the skull to specific cortical regions and induces plastic  
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46 113 changes in the brain and language function in long-term post-stroke aphasia patients. However, its  
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48 114 efficacy is still controversial and needs further confirmation by large-scale clinical trials<sup>24</sup>.  
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54 115 We previously developed a surgical procedure for contralateral C7 transfer from the nonparalyzed  
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56 116 side to the paralyzed side (contralateral C7 to C7 cross nerve transfer [CC7]), after which patients  
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3 117 demonstrated improved motor function and reduced spasticity in the paralyzed arm over 12  
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5 118 months<sup>25</sup>. So far, more than 1,000 patients have undergone this surgery<sup>26</sup>. In addition to arm motor  
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8 119 recovery, the improvement of language was frequently self-reported by patients and caregivers  
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10 120 during the follow-up, and it would occur very rapidly after CC7 treatment. A few days is far from  
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12 121 enough time for the transferred C7 nerve to regenerate<sup>27</sup>; therefore, we assumed that the rapid  
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14  
15 122 improvement of language function was mediated by the C7 neurotomy (NC7) on the paralyzed side  
16  
17 123 (right side) rather than nerve regeneration. During the CC7 operation<sup>28</sup>, to make the C7 nerve on the  
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19 124 paralyzed side can provide more nerve fibre length, we cut the C7 nerve root at the intervertebral  
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22 125 foramen. Based on anatomical research, the anterior and posterior roots converge into spinal nerves  
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24 126 at the intervertebral foramen, and the posterior roots enlarge near the intervertebral foramen to form  
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26 127 ganglia, also known as dorsal root ganglion (DRG)<sup>29 30</sup>. The exact location of neurotomy is at the  
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29 128 transitional junction of the C7 nerve root with DRG<sup>31</sup>. The human C7 nerve contains 80,000  
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31 129 fibers<sup>32</sup>, 94% of which are sensory fibres emitted by DRG<sup>33</sup>. Hence, the neurotomy of the C7 nerve  
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33 130 root at the junction with DRG can block the ascending sensory pathway from the affected limb to  
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36 131 the brain. Based on the anatomy of brain functional areas, we hypothesized that, since the sensory-  
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38 132 motor centre is adjacent to the language centre, if the sensory-motor centre would be changed  
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40 133 artificially by NC7 at the intervertebral foramen, then it is possible to induce the language centre  
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42 134 and produce related functional changes. It may also be that NC7 leads to a change in the  
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45 135 interhemispheric balance, thus, affecting the functional neural circuits of language. We designed  
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47 136 this trial to evaluate the surgical effect of NC7 at the intervertebral foramen on underlying  
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49 137 neuroplasticity in patients with chronic post-stroke aphasia. Meanwhile, the iSLT is used as the  
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52 138 control method we will assess the effect of intensive intervention after 3 weeks and the maintenance  
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54 139 of the effect after 6 months in both groups. Meanwhile, we use neuroimaging methods to provide  
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56 140 objective data as evidence to support our hypothesis.  
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## 60 142 **Aims of the study**

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3 143 The study aims to evaluate the therapeutic efficacy of the NC7 at the intervertebral foramen on  
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6 144 language impairment in patients with chronic post-stroke aphasia. The current paper describes the  
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8 145 design of this study.

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10 146 Our specific objectives are: (1) to evaluate the comparative effectiveness of different interventions,  
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12 147 NC7 plus iSLT (3 weeks) and iSLT (3 weeks) alone, and the further validation of the safety and  
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15 148 long-term effectiveness (6 months) of the NC7 surgical programme. (2) To evaluate the motor and  
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17 149 sensorimotor function of the paralyzed arm and clarify the correlation between motor function and  
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19 150 language function changes postoperatively. (3) To confirm the central mechanism of NC7 at the  
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22 151 intervertebral foramen and access the underlying neuroplasticity via functional neuroimaging  
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24 152 measurements.

## 25 26 153 27 28 154 **METHODS AND ANALYSIS**

### 29 30 155 **Trial design**

31  
32 156 This study is a multicentre, randomised controlled trial with two parallel groups and a 6-month  
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34 157 follow-up. Based on language and motor function analysis, the protocol compares patients with  
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36 158 chronic aphasia treated with the NC7 at the intervertebral foramen and iSLT (Group A), with a  
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38  
39 159 control group participating in iSLT alone (Group B). The participants will be randomly allocated to  
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41 160 one of the two groups (NC7+iSLT group or iSLT alone group) with a ratio of 1:1. The study is  
42  
43 161 conducted in collaboration with the Speech Therapy Committee of the Shanghai Association of  
44  
45 162 Rehabilitation Medicine, and the participants will be recruited from rehabilitation facilities of this  
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47  
48 163 organization. Patients will receive an indication for outpatient rehabilitation treatment at any of the  
49  
50 164 four centres (Supplemental Table 1), based on the eligibility criteria listed below. The potentially  
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52 165 eligible patients will be invited to participate in the study via a text message after signing an  
53  
54  
55 166 informed consent.

### 56 57 167 58 59 168 **Eligibility criteria**

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3 169 Inclusion criteria:  
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6 170 1) Aphasia for over 12 months after a single onset of infarction or haemorrhage of the left  
7  
8 171 hemisphere, confirmed by magnetic resonance imaging;  
9  
10 172 2) Age: 40-65 years, sex: male or female, right-handed, native Chinese speaker;  
11  
12 173 3) Aphasia quotient below 93.8 points assessed by Western Aphasia Battery;  
13  
14 174 4) Severity score assessed by BDAE test: level 1 and above;  
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16  
17 175 5) Good compliance and ability to cooperate with language rehabilitation training;  
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19 176 6) Ability to fully understand and agree with the doctor's treatment plan and sign the informed  
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22 177 consent.

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24 178 Criteria 3 and 4 need to be confirmed by two attending specialists' diagnostic evaluation.  
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26 179 Exclusion criteria:  
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29 180 1) Surgical contraindications (any reason) determined by a qualified anaesthesiologist or clinician;  
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31 181 2) A history of aphasia before the last onset of the stroke;  
32  
33 182 3) Serious, untreated mental illness;  
34  
35 183 4) Aphasia due to neurodegenerative diseases or traumatic brain injury;  
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38 184 5) Presenting contraindications for EEG and MRI evaluation;  
39  
40 185 6) Unable to complete the assessments and rehabilitation required by the study design;  
41  
42 186 7) Severe motor speech disorder and hearing impairment;  
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45 187 8) Having received intensive post-stroke rehabilitation therapy 4 weeks before recruitment.  
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49 189 **Interventions**

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51 190 **NC7 at the intervertebral foramen**  
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53 191 Make a 6-cm long longitudinal incision along the medial border of the sternocleidomastoid muscle  
54  
55 192 on the right side after the cervical plexus under anaesthesia/general anaesthesia (depending on the  
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57 patient's preference and the anaesthesiologist's risk assessment). Carefully separate the structure  
58 193 layer by layer and identify the brachial plexus by marking the C7 nerve with a vessel loop. Next,  
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3 195 the C7 root is mobilized and sectioned as proximally (at the intervertebral foramen) as possible.  
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6 196 Considering that some patients have limb hemiplegia, CC7 surgery may be required to improve  
7  
8 197 limb function at the end of this trial. Therefore, we fix the severed C7 root to the fascia at the  
9  
10 198 junction of the scapulothyoid and sternocleidomastoid muscles with silk thread, making it easier to  
11  
12 199 find and anastomose with the contralateral C7 root during the later CC7<sup>28</sup> surgical intervention.  
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15 200

### 17 201 **iSLT Rehabilitation**

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19 202 Considering previous studies' results, we formulated a 3-week iSLT plan. Speech and language  
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21 203 therapy with a therapist for at least 45 minutes, twice daily, 5 days/week. Additional 1 hour/day  
22  
23 204 self-administrated language-specific training. Patients receive rehabilitation treatment at different  
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25 205 centres, where qualified rehabilitation therapists perform the therapy.  
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29 206

### 31 207 **Study setting**

32  
33 208 This study started on July 2022, participants will be recruited between July 2022 and July 2023.  
34  
35 209 Study completion is expected to be July 2024. A total of 50 patients diagnosed with chronic  
36  
37 210 aphasia and hemiplegia after stroke will be recruited. Patients in the research institutions will  
38  
39 211 receive in-hospital treatment for 3 to 4 weeks, with follow-up assessment at 6 months (Figure 1).  
40  
41 212 Patients will be selected based on the study eligibility criteria on their first visit. Then, eligible  
42  
43 213 patients will be randomly assigned to one of the two groups in different centres. Patients of Group  
44  
45 214 A will receive NC7 immediately after assignment and receive a short-term efficacy assessment 3  
46  
47 215 days later. The total perioperative period is one week. Meanwhile, patients of Group B are awaiting  
48  
49 216 the therapy programme, and also receive a short-term efficacy assessment after 3 days later. The  
50  
51 217 iSLT and upper extremity motor rehabilitation programme are provided for patients in both groups.  
52  
53  
54 218 After a 3-week inpatient intervention, all the patients receive primary endpoint assessments, and then  
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56 219 they continue to receive conventional low-intensity SLT at home or in other centres. For arm motor  
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3 220 function follow-up, patients are guided to perform the rehabilitation programme consistently while  
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6 221 a therapist or caregiver records the intensity and duration of the therapy. Six months later, all  
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8 222 patients will receive an interim evaluation by a trained therapist from an independent team on their  
9  
10 223 second visit. Afterwards, the NC7 and postoperative rehabilitation programme, which is consistent  
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12 224 with Group A, are performed in patients of Group B. Likewise, these patients will receive a short-  
13  
14  
15 225 term and long-term follow-up for efficacy assessment. The schedule of enrolment, interventions and  
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17 226 assessments are presented in Table 1.

## 21 228 **Participant timeline**

23 229 The schedule is presented in Table 1.

25 230 **Table 1. Timeline schedule of enrolment, interventions and assessments.**

26 231

27 <b>NC7+iSLT (Group A: experimental group)</b>					
28 <b>TIMEPOINT</b>	29 <b>Visit 1 (Eligibility screen)</b>	30 <b>Visit 2 (Baseline)</b>	31 <b>Visit 3 (3d+1d post- NC7)</b>	32 <b>Visit 4 (3w±3d post iSLT onset)</b>	33 <b>Visit 5 (24w±7d post iSLT end)</b>
34 <b>Informed consent</b>	√				
35 <b>Inclusion and Exclusion Criteria</b>	√				
36 <b>Demographic variables</b> Age, sex, education, etc.	√				
37 <b>General physical examination</b>	√				
38 <b>Primary outcome</b>		√	√	√	√
39 <b>Secondary outcomes</b>		√	√	√	√
40 <b>Safety outcomes</b>		√	√	√	√
41 <b>Brain plasticity evaluation</b>		√		√	√
42 <b>Endpoint</b>			√	√	√
43 <b>Adverse events assessment</b>			√	√	√
44 <b>iSLT alone (Group B: control group)</b>					

TIMEPOINT	Visit 1 (Eligibility screen)	Visit 2 (Baseline)	Visit 3 (3d+1d post- treatment waiting onset)	Visit 4 (3w±3d post iSLT onset)	Visit 5 (24w±7d post iSLT end)
Informed consent	√				
Inclusion and Exclusion Criteria	√				
Demographic variables Age, sex, education, etc.	√				
General physical examination	√				
Primary outcome		√	√	√	√
Secondary outcomes		√	√	√	√
Safety outcomes		√	√	√	√
Brain plasticity evaluation		√		√	√
Endpoint			√	√	√
Adverse events assessment			√	√	√

(d) day, (w) week, (m) month.

(NC7) C7 neurotomy at the intervertebral foramen, (iSLT) intensive speech and language therapy.

## Randomization and blinding

This study's stratified block randomization process is done by using an interactive web response system (IWRS), and the stratified factor is the centre (Huashan Hospital, Fudan University; Shanghai Pudong Hospital; Huadong Hospital affiliated to Fudan University, Shanghai Xuhui Central Hospital). The blinding method of this clinical trial is applied in the outcome evaluation stage. During the onsite evaluation process, patients will be required to wear a cervical collar to cover the neck (wound site of patients in the experimental group), which will be videotaped. An independent team of trained therapists will conduct the video recording and performance scoring process.

## Outcomes measures

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3 247 The primary outcome is the change in total score on the Boston naming test (BNT) scale of Group  
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6 248 A and B from baseline (T0) to post-intervention, week 4(T2). BNT is a classic measurement tool  
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8 249 for evaluating language function; the international version is BNT-60. The BNT scale shows a high  
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10 250 concurrent validity with other standard naming ability assessment tools, and it is particularly  
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12 251 suitable in the post-acute/chronic phase after stroke aphasia. In this study, we chose the validated  
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15 252 Chinese version of BNT<sup>34 35</sup>.  
16  
17 253 The secondary outcomes include aphasia quotient, daily communication (Communication Activities  
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19 254 of Daily Living–Third Edition [CADL-3]), activities of daily living (Barthel Index), speech  
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21  
22 255 language function assessment (ICF<sup>36</sup> speech language function assessment), post-stroke depression  
23  
24 256 assessment (Hamilton Rating Scale for Depression, HRSD) and safety outcomes in different  
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26 257 groups. Assessments performed to collect data for the primary, secondary, and safety outcomes are  
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29 258 listed in Table 2.

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31 259

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33 260 **Table 2. Assessments performed to collect data for the primary, secondary, and safety**  
34 261 **outcomes**

Variable	Measure
<b>Primary outcome</b>	
Naming ability	Change from baseline in Boston Naming Test (BNT) score. The BNT scale is a performance-based measure commonly used to assess the visual confrontation naming ability among adults with aphasia. Participants are shown pictures of common objects and asked to name each stimulus item within 20 seconds: minimum score of 0, maximum score of 60. Higher scores mean better outcomes in naming ability.
<b>Secondary outcome</b>	
Aphasia quotient	Change from baseline in WAB score. The WAB scale is a weighted average of all subtest scores relating to spoken language. It is a sum of all subtest scores from the first four parts of the WAB (spontaneous speech, Auditory verbal comprehension, Repetition, Naming and word finding), recording the total average score and standard deviation. The total range is 0-100 (higher scores indicating better performance).

59  
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Daily communication	Change from baseline in the Communication Activities of Daily Living–Third Edition (CADL-3). The CADL-3 scale contains 50 items assessing functional communication skills in seven areas of adults with neurogenic communication disorders. Participants receive a score of 0, 1, or 2 for each item. Higher scores reflect better communicative success.
Speech language function assessment	Change from baseline in ICF speech language function assessment. Aphasia-adapted ICF speech language function assessment for self-evaluation of communication functions, participation, and activity. Minimum score -2, maximum score +2. Higher scores mean better outcome in quality of life.
Activities of daily living	Change from baseline in Barthel Index (BI) score.
Post-stroke Depression assessment	Change from baseline in Hamilton Rating Scale for Depression (HRSD-24) score.
<b>Safety outcomes</b>	
Muscle strength	Change from baseline in Medical Research Council grading system score.
Spasticity	Change from baseline in the Modified Ashworth Scale (MAS) score.
Range of motion	Change from baseline in range of motion of the main joints of the upper limbs score.
Sensory function assessment	Change from baseline in the tactile sensory threshold and 2-point discrimination score.

### Brain plasticity evaluation

The explorative evaluations included brain functional plasticity detection with functional magnetic resonance imaging (MRI) and EEG evaluations. The resting-state, task-designed functional and structural MRI using a GE 3.0 T MRI scanner (MR750) will be collected at baseline, 3-week and 6-month follow-up. In task-designed MRI and EEG evaluations, picture naming tasks and semantic prediction tasks are used to assess patients' recovery and the central plasticity mechanism of the recovery.

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**Adverse events**

The safety of patients will be monitored at each study visit point. Patients will receive study information containing explicit details on whom to contact in case of an adverse event. Investigators will record all descriptions of adverse events during each patient visit. In this clinical trial, death, life-threatening, severe deterioration of health, etc., will be considered severe adverse events (SAE). Patients with SAEs will withdraw from the clinical trial, as it would be unsafe to continue the trial procedure. Once SAE occurs, investigators should take immediate treatment measures to ensure the safety of patients and report to the institutional review board and relevant competent authorities within 24 hours of the occurrence of SAE.

280

**Data collection and management**

Data are collected via a case report form developed at the outset of the study. The data administrator is responsible for reviewing and managing the entered data. After the data is checked and the database is confirmed correct, it will be locked and submitted for statistical analysis. The original data of the functional neuroimage will be presented as a disk, and the data without patients' personal information will be saved and analysed.

**Analyses****Sample size**

This study intends to use the change of the naming score from baseline to post-intervention as the primary outcome. According to the literature<sup>17 20</sup>, the naming score can be improved after intensive speech therapy and verified after non-invasive brain stimulation therapy<sup>22 23</sup>. In the unpublished data which is a phase-I cohort study including post-stroke aphasia patients who received NC7 plus iSLT, the score of the patients' naming ability evaluated by Boston Naming Test (BNT) was increased by 11.0 points in average, while the patients who received iSLT alone increased by 5.7

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3 295 points in average from the literature review<sup>37</sup>. According to results from our phase-I study, the  
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6 296 standard deviation was 6.0. A 2-sided 0.05 level of significance and a sample size of 40 patients (20  
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8 297 per group) provided 80% statistical power to demonstrate this difference in the change of BNT  
9  
10 298 score from baseline. Considering a drop-out rate of 15%, we will recruit a total of 50 patients (25  
11  
12 299 per group).

### 17 301 **Statistical analysis**

19 302 Analyses of primary endpoints will be performed in the full analysis set, which includes all random  
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21 303 patients who received study treatment. Per-protocol set is defined as all patients completing the  
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24 304 study without major protocol deviation. Safety is evaluated in all randomly assigned patients  
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26 305 receiving study treatment and analysed using descriptive statistics.

28 306 Categorical data are presented as frequency and percentage, and continuous data are described by  
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31 307 mean (standard deviation) or median (interquartile range). Between-group comparisons of changes  
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33 308 from baseline in primary and secondary outcomes are performed using analysis of covariance. The  
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35 309 baseline value and centre are covariates. Generalized estimating equation models are used to  
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38 310 analyse the longitudinal data between groups. Subgroup analysis includes study centre, type of  
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40 311 aphasia, aetiology of aphasia, and severity of aphasia. Sensitivity analysis is performed on missing  
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42 312 data for the primary endpoint. All hypothesis tests are two-sided, and values of  $P < 0.05$  is  
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44  
45 313 considered statistically significant.

### 49 315 **ETHICS AND DISSEMINATION**

51 316 Ethical approval for this trial was granted by the Institutional Review Board of Huashan Hospital,  
52  
53  
54 317 Fudan University (No. KY2021-592), and by the institutional review boards of all participating  
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56 318 institutions (Supplemental Table 1). All patients will sign an informed consent prior to entry into  
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58 319 the study. Patients may withdraw from the study at any time. Important protocol modifications will  
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320 be communicated to the relevant members of the research team. The procedure will be performed  
321 following the principles described in the declaration of Helsinki.

322

### 323 **Patient and public involvement**

324 We asked for the advice of patients with chronic aphasia after stroke in rehabilitation facilities that  
325 meet the physical and emotional needs of the population. The doctors and therapists from the  
326 rehabilitation facilities will provide support for the recruitment. The study results will be  
327 disseminated to the public upon completion of the trial and the individual test results will be  
328 provided to patients upon request.

329

### 330 **DISCUSSION**

331 Due to the high morbidity and heavy disease burden of stroke in China<sup>38</sup>, there is an urgent need for  
332 effective treatments of chronic post-stroke aphasia. The current manuscript describes the  
333 methodology of a trial design for the effects of NC7 on language impairment symptoms in patients  
334 with chronic post-stroke aphasia. This study bears major importance because it could provide  
335 evidence for the validity of a novel therapeutic strategy for improving language function while  
336 diminishing dysfunctions after stroke.

337 This study focuses on the evaluation of postoperative language function. The language function can  
338 be assessed by naming tests, communication ability assessments, etc. Patients with aphasia who  
339 receive iSLT or non-invasive peripheral stimulation can exhibit improvements in naming ability<sup>39</sup>  
340 and social communication<sup>18</sup>, but the effect sizes were usually modest. In the previous study, we  
341 found that the naming ability of patients after CC7 was significantly improved, and many other  
342 researchers also used the correct spontaneous naming scores as the only BNT-related index for  
343 evaluating language function<sup>40 41</sup>. In this study, we use the BNT scale as an evaluation index for  
344 language function for the primary outcome, and we will use WAB, CADL Communication Scale,

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3 345 ADL Scale, and Post-Stroke Depression Scale scores as secondary indicators in the aspects of  
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6 346 language repetition, listening comprehension, communication ability, daily life, and psychology.  
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8 347 The ICF speech and language function assessment can detect the degree of changes in voice  
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10 348 intonation, oral motor ability, articulation intelligibility, and oral expression of patients to exclude  
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12 349 the possible reduction of spasticity after neurotomy for the interference with study results.  
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14  
15 350 The CC7 was first invented by Gu et al.<sup>42-44</sup> to treat limb dysfunction after brachial plexus injury,  
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17 351 and the follow-up work<sup>45 46</sup> showed neuroplastic changes between the hemispheres after surgery.  
18  
19 352 Based on this theoretical perspective, Xu originally proposed the scientific viewpoint that "One  
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22 353 hemisphere controls both limbs" and expanded the development of the "contralateral C7 nerve  
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24 354 transfer" to "contralateral C7 to C7 cross nerve transfer" for treating central hemiplegia<sup>25 47 48</sup>. Our  
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26 355 previous investigations suggested the possible correlation between CC7 and the improvement of  
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28 356 chronic aphasia, an effect occurring in the early postoperative period; thus, the possibility of  
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31 357 aphasia recovery after NC7 at the intervertebral foramen caught our attention. In this study, we  
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33 358 measured muscle strength, joint range of motion, upper limb MAS score and sensory assessment as  
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35 359 safety indicators to evaluate the effect of the NC7 on the right side. If the NC7 does improve  
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38 360 language function with no physical dysfunction, it will provide an entirely novel perspective for the  
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40 361 treatment of chronic post-stroke aphasia. However, the mechanisms involved in NC7 effectiveness  
41  
42 362 in chronic aphasia are not fully understood. We consider that this clinical phenomenon of language  
43  
44 363 function improvement is related to NC7 stimulating neuroplasticity. This requires more objective  
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47 364 functional imaging evidence to confirm. Several recent publications review the mechanisms of  
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49 365 aphasia recovery. In some cases, the therapy mechanisms<sup>49 50</sup> are evidenced by changes in task-  
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51 366 related brain activations or changes in functional connectivity within functional networks<sup>51 52</sup>. Here,  
52  
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54 367 we use fMRI and EEG methods in relation to the naming ability and semantic prediction to  
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56 368 investigate the neural and physiological states induced by changes in the language function after  
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58 369 NC7.  
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3 370 In conclusion, this is the first RCT to evaluate the surgical effect in patients with chronic post-  
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6 371 stroke aphasia for whom there is no effective treatment available. If found to be efficient, this  
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8 372 strategy could be regularly implemented due to its easy application and low cost. Moreover, larger  
9  
10 373 trials could be extended to other diseases with a central nerve injury to assess for this strategy's  
11  
12 374 efficiency on language and other functions. Once our hypothesis is confirmed, this trial will provide  
13  
14  
15 375 important evidence for supporting NC7 at the intervertebral foramen as a novel treatment approach  
16  
17 376 for chronic aphasia. A limitation of this study is that it is not double-blind but evaluator-blind, and  
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19 377 the experimental group may involve a minor placebo effect. To offset the short-term placebo effect  
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22 378 after surgery, we conducted a secondary endpoint assessment at 6 months. At that time, the patient's  
23  
24 379 placebo effect due to invasive interventions will be greatly reduced.  
25  
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27 380

## 28 29 381 **Abbreviations list**

30  
31 382 RCT = randomised controlled trials; CC7 = contralateral C7 to C7 cross nerve transfer; NC7 = C7  
32  
33  
34 383 neurotomy; iSLT = intensive speech and language therapy; DRG=dorsal root ganglion; BDAE=  
35  
36 384 Boston Diagnostic Aphasia Examination; BNT = Boston naming test; WAB = Western Aphasia  
37  
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39 385 Battery; CADL = Communication Activities of Daily Living; ADL= Activity of Daily Living;  
40  
41 386 ICF=International classification of Functioning, Disability and Health; HRSD= Hamilton Rating  
42  
43 387 Scale for Depression, EEG = Electroencephalography; fMRI = functional magnetic resonance  
44  
45 388 imaging; SAE = Severe Adverse Events.  
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## 49 50 390 **Competing Interests**

51 391 None declared.  
52  
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## 55 56 57 393 **Patient consent for publication**

58  
59 394 Not required.  
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7  
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14  
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21

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25  
26 405 University and all the participating institutions.

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28 406  
29

## 30 407 **Contributors**

31  
32 408 WX is the principal investigator of this study and refined the protocol. TL and JF wrote the  
33  
34 409 manuscript and contributed to the design of the study. ML, the medical statistician for the study,  
35  
36  
37 410 contributed to the statistical design and ethical approval. WC contributed to brain plasticity  
38  
39 411 evaluation design and guidance. YG participated in the concept and design of the study. RH, XM,  
40  
41 412 WQ, YZ, XC, LD have revised the protocol critically for multicentre intellectual content. All  
42  
43  
44 413 authors read and approved the final manuscript.

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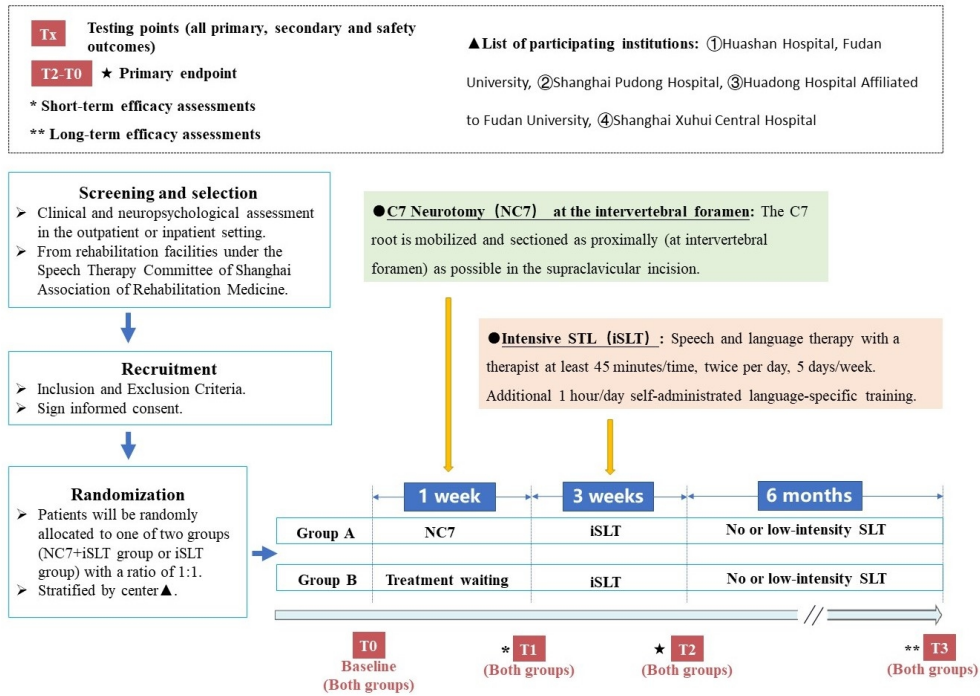
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## Figure caption

**Figure 1.** Trial design in detail and patients flow chart.



Trial design in detail and patients flow chart.

355x248mm (96 x 96 DPI)

**Supplemental Table 1. List of all participating institutions and institutional review boards in this trial**

<b>Major research institution</b>	<b>Name of institutional review board</b>
Huashan Hospital, Fudan University	Institutional Review Board of Huashan Hospital Affiliated to Fudan University
<b>Sub-centre research institution</b>	<b>Name of institutional review board</b>
Shanghai Pudong Hospital	Academic Ethics Committee of Shanghai Pudong Hospital
Huadong Hospital Affiliated to Fudan University	Ethics Committee of Huadong Hospital Affiliated to Fudan University
Shanghai Xuhui Central Hospital	Shanghai Xuhui Central Hospital Ethics Committee



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

Section/item	Item No	Description	Addressed on page number
<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 _____
	2b	All items from the World Health Organization Trial Registration Data Set	_____ NA _____
Protocol version	3	Date and version identifier	_____ 1-2 _____
Funding	4	Sources and types of financial, material, and other support	_____ 18 _____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____ 1,18 _____
	5b	Name and contact information for the trial sponsor	_____ NA _____
	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	_____ NA _____
	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)	_____ 6-7, 13-15 _____

1 **Introduction**

2

3 Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention \_\_\_\_\_ 3-6 \_\_\_\_\_

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6 6b Explanation for choice of comparators \_\_\_\_\_ 3-6 \_\_\_\_\_

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8 Objectives 7 Specific objectives or hypotheses \_\_\_\_\_ 6, 7 \_\_\_\_\_

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10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) \_\_\_\_\_ 6,7 \_\_\_\_\_

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14 **Methods: Participants, interventions, and outcomes**

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16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained \_\_\_\_\_ 8,9 \_\_\_\_\_

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19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) \_\_\_\_\_ 6-8 \_\_\_\_\_

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22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered \_\_\_\_\_ 7-9 \_\_\_\_\_

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25 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) \_\_\_\_\_ 13 \_\_\_\_\_

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28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) \_\_\_\_\_ NA \_\_\_\_\_

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31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial \_\_\_\_\_ 7-9 \_\_\_\_\_

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34 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 \_\_\_\_\_ 10-13 \_\_\_\_\_

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40 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) \_\_\_\_\_ 9,10 \_\_\_\_\_

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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____13-14_____
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____8,9_____
5				
6				
7	<b>Methods: Assignment of interventions (for controlled trials)</b>			
8	Allocation:			
9				
10	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____10-13_____
11				
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____8-10_____
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____NA_____
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____10_____
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA_____
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31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____13,14_____
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39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____NA_____
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____ 13,14 _____
2				
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5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____ 14,15 _____
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____ 14 _____
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____ NA _____
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14	<b>Methods: Monitoring</b>			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____ NA _____
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____ NA _____
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____ 13 _____
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____ NA _____
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____ 14,15 _____
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37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____ NA _____
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ NA _____
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ NA _____
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7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____ NA _____
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____ 17 _____
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 13,14 _____
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16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____ NA _____
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____ 15 _____
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ NA _____
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ NA _____
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29	<b>Appendices</b>			
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31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Supplemental Material__
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____ NA _____
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37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.  
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# BMJ Open

## Effect and safety of C7 neurotomy at the intervertebral foramen in patients with chronic post-stroke aphasia: A multicentre, randomised, controlled study protocol

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Neurology
Secondary Subject Heading:	Neurology, Surgery
Keywords:	Stroke < NEUROLOGY, Neurosurgery < SURGERY, Clinical trials < THERAPEUTICS

SCHOLARONE™  
Manuscripts

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3 1 **TITLE PAGE**  
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5 2 **Effect and safety of C7 neurotomy at the intervertebral foramen in patients with chronic post-**  
6 **stroke aphasia: A multicentre, randomised, controlled study protocol**  
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8

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42 33 **Keywords:** chronic post-stroke aphasia, C7 neurotomy (NC7) at the intervertebral foramen,  
43 34 intensive speech and language therapy (iSLT), neuroplasticity  
44 35

45 36 **Word count: 3889**  
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## ABSTRACT

- **Introduction:** Aphasia affects many stroke survivors; therefore effective treatments are urgently needed. Preliminary clinical findings have suggested an association between Contralateral C7 to C7 Cross Nerve Transfer (CC7) and recovery from chronic aphasia. Randomised controlled trials supporting the efficacy of C7 neurotomy (NC7) are lacking. This study will explore the efficacy of NC7 at the intervertebral foramen for improving chronic post-stroke aphasia.
- **Methods and analysis:** This study protocol reports a multicentre, randomised, assessor-blinded active-controlled trial. A total of 50 patients with chronic post-stroke aphasia for over one-year and with a aphasia quotient calculated by Western Aphasia Battery Aphasia Quotient (WAB-AQ) score below 93.8 will be recruited. Participants will be randomly assigned to one of two groups (25 individuals each) to receive NC7 plus intensive speech and language therapy (iSLT), or iSLT alone programme. The primary outcome is the change in Boston Naming Test score from baseline to the first follow-up after NC7 plus 3 weeks of iSLT, or iSLT alone. The secondary outcomes include the changes in the WAB-AQ, Communication Activities of Daily Living (CADL-3), ICF speech language function, Barthel Index (BI), Stroke Aphasic Depression Questionnaire-hospital version (SADQ-H10), and sensory-motor assessments. The study will also collect functional imaging outcomes of naming and semantic violation tasks through functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG) to evaluate the intervention-induced neuroplasticity.
- **Ethics and dissemination:** This study was approved by the institutional review boards of Huashan Hospital, Fudan University, and all participating institutions. The study findings will be disseminated through peer-reviewed publications and conference presentations.

**Trial registration:** ChiCTR2200057180

## ARTICLE SUMMARY

### Strengths and limitations of this study

- This will be the first multicentre neurosurgery randomised controlled trial aimed at improving language function in patients with chronic post-stroke aphasia.
- This study will explore the possibility of a new strategy to improve multiple dysfunctions after central nervous system injury, based on peripheral neurosurgery and traditional rehabilitation treatments.
- A limitation of this study is that it will be evaluator-blinded rather than double-blinded, and that the experimental group may receive a minor placebo effect.

## 74 INTRODUCTION

### 75 Background and rationale

76 Aphasia refers to a collection of acquired receptive and expressive language deficits that arise in  
77 many neurological diseases or after trauma and is most commonly seen following left hemisphere  
78 stroke<sup>1</sup>. Globally, more than 10 million new stroke cases are reported each year<sup>2</sup>, with at least one-  
79 third of these patients experiencing symptoms of aphasia<sup>3</sup> – one of the most devastating symptoms  
80 in stroke survivors<sup>4 5</sup>. Aphasia is responsible for substantial costs for individuals with stroke during  
81 the acute and chronic phases and is an independent predictor of subsequent functional dependence  
82 and death<sup>3 6</sup>. The presence of aphasia predicts care and rehabilitation needs<sup>7</sup> as well as and the  
83 likelihood of failure to return to work<sup>8</sup>. Language function in patients with post-stroke aphasia  
84 recovers spontaneously to varying degrees<sup>9</sup>. It's generally recognised that spontaneous recovery in  
85 language function reaches a plateau–6–9 months after the first onset of stroke, and further  
86 improvements afterwards are few and negligible<sup>10 11</sup>. During recovery, both the subtype and  
87 severity of aphasia change over time and patients may progress from sensory aphasia to conduction  
88 aphasia to naming aphasia, and to “recovered”<sup>12</sup>. Nevertheless, this “recovered” status may also  
89 involve a mild, residual impairment that could be detected by a sensitive assessment<sup>13</sup>. However,  
90 some forms of aphasia persist into the chronic phase in at least half of the patients<sup>14</sup>.

91 Although most aphasia therapy studies have enrolled patients with chronic stroke, conceivably,  
92 earlier aphasia therapy is also effective, as it has achieved good results after stroke<sup>15</sup>. Common  
93 aphasia rehabilitation treatments include classic speech-language rehabilitation training, low-  
94 frequency electrical stimulation therapy, repetitive transcranial magnetic stimulation and  
95 transcranial direct current stimulation. Many clinical studies<sup>16 17</sup> have shown that speech and  
96 language therapy (SLT) effectively improves communication, reading, writing, and language  
97 expression in patients with post-stroke aphasia, and high-intensity and long-term mode may have  
98 better effects<sup>18</sup>. A large-scale randomised control trial (RCT) reported that, 3 weeks of intensive  
99 speech and language therapy (iSLT) showed improvements in patients with chronic post-stroke

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3 100 aphasia and significantly enhanced verbal communication among people aged 70 years or  
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6 101 younger<sup>17</sup>. This beneficial outcome could be maintained for up to 6 months after treatment. Stahl<sup>19</sup>  
7  
8 102 further determined the optimal daily dosage and total duration of iSLT, reporting no added value  
9  
10 103 from > 2h of daily SLT within 4 weeks. In addition, non-invasive brain stimulation therapy is  
11  
12 104 widely used in the rehabilitation of various neurological diseases. Transcranial direct current  
13  
14 105 stimulation (tDCS) uses electrode pads to deliver a weak direct current to specific brain regions,  
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16  
17 106 which can affect the function of the cerebral cortex and help improve the accuracy of noun naming  
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19 107 in patients with aphasia<sup>20-22</sup>. However, sufficient data on the optimal sample size and a strict  
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21  
22 108 methodology. Low-frequency repetitive transcranial magnetic stimulation (rTMS) is the regular and  
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24 109 repeated application of a pulsed magnetic field that briefly penetrates the skull targeting specific  
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26 110 cortical regions; this induces plastic changes in the brain and language function in patients with  
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28 111 long-term post-stroke aphasia. However, its efficacy remains controversial and warrants further  
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30  
31 112 confirmation through large-scale clinical trials<sup>23</sup>.

32  
33 113 We previously developed a surgical procedure for contralateral C7 transfer from the nonparalysed  
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35 114 to the paralysed side (contralateral C7 to C7 cross nerve transfer [CC7]), after which patients with  
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37  
38 115 stroke demonstrated improved motor function and reduced spasticity in the paralysed arm over 12  
39  
40 116 months<sup>24</sup>. To date, more than 1,000 patients have undergone this surgery<sup>25</sup>. In addition to arm  
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42 117 motor recovery, language improvement was frequently self-reported by patients and caregivers  
43  
44 118 during follow-up, and it occurred very rapidly after CC7 treatment. A few days are by far not  
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46  
47 119 sufficient for the transferred C7 nerve to regenerate<sup>26</sup>; therefore, we assumed that the rapid  
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49 120 improvement in language function was mediated by the C7 neurotomy (NC7) on the paralysed side  
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51 121 (right side), rather than nerve regeneration. During the CC7 operation, we cut the C7 nerve root at  
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53  
54 122 the intervertebral foramen to ensure that the C7 nerve on the paralysed side would provide more  
55  
56 123 nerve fibre length<sup>27</sup>. The anterior and posterior roots converge into spinal nerves at the  
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58 124 intervertebral foramen, and the posterior roots enlarge near the intervertebral foramen to form  
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1  
2  
3 125 ganglia, also known as the dorsal root ganglion (DRG)<sup>28 29</sup>. The exact location of the neurotomy  
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5  
6 126 was the transitional junction of the C7 nerve root with the DRG <sup>30</sup>. The human C7 nerve contains  
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8 127 80,000 fibers<sup>31</sup>, 94% of which are sensory fibres emitted by the DRG<sup>32</sup>. Hence, neurotomy of the  
9  
10 128 C7 nerve root at the junction with the DRG could block the ascending sensory pathway from the  
11  
12 129 affected limb to the brain. Based on the anatomy of the brain functional areas, we hypothesized that,  
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14  
15 130 since the sensory-motor centre is adjacent to the language centre, if the sensory-motor centre is  
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17 131 artificially changed by NC7 at the intervertebral foramen, it maybe possible to stimulate the  
18  
19 132 language centre and achieve relevant functional changes. NC7 may also leads to a change in  
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21  
22 133 interhemispheric balance, thus affecting the functional neural circuits of language. We designed this  
23  
24 134 trial to evaluate the surgical effect of NC7 at the intervertebral foramen on the underlying  
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26 135 neuroplasticity in patients with chronic post-stroke aphasia. Meanwhile, the iSLT will be used as  
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28  
29 136 the control method to assess the effect of the intensive intervention after 3 weeks and the  
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31 137 maintenance of the effect after 6 months in both groups. Neuroimaging methods will be  
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33 138 simultaneously used to obtain objective data to test our hypothesis.

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35 139

### 37 140 **Aims of the study**

38  
39 141 This study will to evaluate the therapeutic efficacy of NC7 at the intervertebral foramen for on  
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41 142 language impairment in patients with chronic post-stroke aphasia. This paper describes the related  
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44 143 study design.

45  
46 144 Our objectives are: (1) to evaluate the efficacy of NC7 plus iSLT (3 weeks) compared to iSLT (3  
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48 145 weeks) alone, as well as the safety and long-term stability of NC7 outcomes. (2) To explore the  
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50 146 possible central plastic mechanism of improvement after NC7 plus iSLT using functional  
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52  
53 147 neuroimaging measurements.

54  
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## 56 57 149 **METHODS AND ANALYSIS**

### 58 59 150 **Trial design**

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3 151 This study will be a multicentre, randomised, assessor-blinded, active-controlled trial. The  
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6 152 participants will be randomly allocated to either group (NC7+iSLT group or iSLT alone group)  
7  
8 153 with a ratio of 1:1 at the four participating centres (Supplemental Table 1). Patients in Group A will  
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10 154 be treated with NC7 at the intervertebral foramen combined with 3-week's iSLT, and patients in  
11  
12 155 Group B will be treated with 3-week's iSLT alone. The participants will be recruited from the  
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15 156 rehabilitation facilities, outpatient department, or through the collaboration with the Speech  
16  
17 157 Therapy Committee of the Shanghai Association. Eligible patients will be invited to participate in  
18  
19 158 this study and will be asked to sign informed consent.  
20  
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22 159

### 23 24 160 **Eligibility criteria**

25  
26 161 The inclusion criteria are the following:

- 27  
28 162 1) aphasia for over 12 months after a single onset of infarction or haemorrhage of the left  
29  
30 163 hemisphere, confirmed by magnetic resonance imaging;
- 31  
32 164 2) of 40–65 years, male or female sex, right-handed, native Chinese speakers;
- 33  
34 165 3) Western Aphasia Battery Aphasia Quotient (WAB-AQ) score below 93.8 points;
- 35  
36 166 4) severity score assessed using the BDAE test of level 1 and above;
- 37  
38 167 5) good compliance and ability to cooperate with language rehabilitation training;
- 39  
40 168 6) ability to understand fully and agree with the doctor's treatment plan and sign the informed  
41  
42 169 consent.

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45  
46 170 Criteria 3 and 4 will to be confirmed through the diagnostic evaluations of two attending specialists.

47  
48  
49 171 Exclusion criteria are the following:

- 50  
51 172 1) any surgical contraindication, determined by a qualified anaesthesiologist or clinician;
- 52  
53 173 2) history of aphasia before the last onset of a stroke;
- 54  
55 174 3) serious, untreated mental illness;
- 56  
57 175 4) aphasia due to neurodegenerative diseases or traumatic brain injury;
- 58  
59 176 5) contraindications for EEG and MRI evaluation;

- 1  
2  
3 177 6) inability to complete the assessments and rehabilitation required per study design;  
4  
5  
6 178 7) severe motor speech disorder and hearing impairment;  
7  
8 179 8) having received intensive post-stroke rehabilitation therapy 4 weeks before recruitment.  
9

10 180

## 12 181 **Interventions**

### 14 182 **NC7 at the intervertebral foramen**

16 183 A 6-cm long longitudinal incision will be made along the medial border of the sternocleidomastoid  
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18  
19 184 muscle on the right side after the cervical plexus, under local /general anaesthesia (depending on the  
20  
21 185 patient's preference and the anaesthesiologist's risk assessment). The structure will be carefully  
22  
23 186 separated layer-by-layer and the brachial plexus will be identified by marking the C7 nerve with a  
24  
25  
26 187 vessel loop. The C7 root will be mobilised and sectioned proximally at the intervertebral foramen.  
27  
28 188 Considering that some patients have limb hemiplegia, CC7 surgery may be required to improve  
29  
30 189 limb function by the end of this trial. Therefore, we will fix the severed C7 root to the fascia, at the  
31  
32  
33 190 junction of the scapulothyoid and sternocleidomastoid muscles, with a silk thread; this will facilitate  
34  
35 191 retrieval and anastomosis with the contralateral C7 root during later CC7 surgical intervention<sup>27</sup>.  
36

37 192

### 39 193 **iSLT Rehabilitation**

41  
42 194 Base on previous studies, we formulated a 3-week iSLT plan. Speech and language therapy will be  
43  
44 195 performed by a therapist for at least 45 min, twice daily, 5 days a week. The intervention will also  
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46 196 involve an additional 1 hour/day of self-administrated language-specific training. The patients will  
47  
48  
49 197 receive rehabilitation treatment at different centres from qualified rehabilitation therapists.  
50

51 198

### 53 199 **Study setting**

55 200 This study will begin in July 2022, and the participants will be recruited between July 2022 and  
56  
57  
58 201 July 2023. The study is expected to be completed in July 2024. Fifty patients diagnosed with  
59  
60 202 chronic aphasia and hemiplegia after stroke will be recruited. The treatment and visit plans are

shown in Figure 1. Patients will be selected on their first visit according to the eligibility criteria. Eligible patients will be randomly assigned to one of the two groups at different centres. The patients in Group A will receive NC7 after baseline assignment and the first assessment on day 3 (+1). The iSLT treatment for Group A will starts 1 week after NC7 surgery. Meanwhile, the patients in Group B will be awaiting the therapy programme, and receive a short-term efficacy assessment after 3(+1) days. These patients will undergo the same iSLT programme as patients in Group A. Three weeks after the iSLT programme, all patients will undergo the second follow-up (3 weeks  $\pm$  3 days after iSLT commencement). All patients will undergo long-term evaluation 6 months after iSLT commencement. The schedules for enrolment, interventions and assessments are presented in Table 1.

### Participant timeline

Table 1 shows the overall study timeline including enrolment, intervention, and assessment schedule.

**Table 1. Timeline of enrolment, intervention and assessment schedule.**

NC7+iSLT (Group A: Experimental group)					
TIMEPOINT	Visit 1 (Eligibility screening)	Visit 2 (Baseline)	Visit 3 (3d+1d post-NC7)	Visit 4 (3w $\pm$ 3d post-iSLT onset)	Visit 5 (24w $\pm$ 7d post-iSLT onset )
Informed consent	√				
Inclusion and Exclusion Criteria scrutiny	√				
Demographic information	√				
General physical examination	√				
Primary outcome		√	√	√	√
Secondary outcomes		√	√	√	√
Safety outcomes		√	√	√	√
Brain plasticity evaluation		√		√	√

<b>iSLT alone (Group B: Control group)</b>					
<b>TIMEPOINT</b>	<b>Visit 1 (Eligibility screening)</b>	<b>Visit 2 (Baseline)</b>	<b>Visit 3 (3 d+1 d, waiting periods onset)</b>	<b>Visit 4 (3 w±3 d post-iSLT onset)</b>	<b>Visit 5 (24 w ± 7 d post- iSLT onset )</b>
<b>Informed consent</b>	√				
<b>Inclusion and Exclusion Criteria ascertainment</b>	√				
<b>Demographic information</b>	√				
<b>General physical examination</b>	√				
<b>Primary outcome</b>		√	√	√	√
<b>Secondary outcomes</b>		√	√	√	√
<b>Safety assessment</b>		√	√	√	√
<b>Brain plasticity evaluation</b>		√		√	√

Abbreviations: d, day; w, week; m, month; NC7, C7 neurotomy at the intervertebral foramen; iSLT, intensive speech and language therapy.

### **Randomization and blinding**

This study's stratified block randomization process will be performed using an interactive web response system; the stratified factor will be the centre: Huashan Hospital, Fudan University; Shanghai Pudong Hospital; Huadong Hospital affiliated to Fudan University; or Shanghai Xuhui Central Hospital. Because the intervention in this study includes surgery at the neck, the assessor-blinded method will be applied at the outcome evaluation stage. All patients will be required to wear a cervical collar to cover their neck during each evaluation, and the evaluation process which will be videotaped. A third-party independent team consisting of two trained evaluators will conduct the language function final scoring based on the videos.

### **Outcome measures**

The primary outcome is the change in the total score of the Boston Naming Test (BNT-60) scale of Groups A and B, from baseline (Visit 2) to post-intervention (Visit 4). The BNT is a classic

236 measurement tool for evaluating language function; BNT-60 is the international version. The BNT  
 237 scale shows high concurrent validity with other standard naming ability assessment tools and is  
 238 particularly suitable for the post-acute/chronic phase after stroke aphasia. In this study, we used  
 239 validated Chinese version of the BNT<sup>33 34</sup>.

240 Secondary outcomes include aphasia quotient, daily communication (using the Communication  
 241 Activities of Daily Living–Third Edition [CADL-3] score), activities of daily living (using the  
 242 Barthel Index), speech language function assessment (using the ICF<sup>35</sup> speech language function  
 243 assessment), post-stroke depression assessment (using the SADQ-H10) and surgical safety-related  
 244 outcomes. The assessments performed to collect data on primary, secondary, and surgical safety  
 245 outcomes are listed in Table 2.

247 **Table 2. Assessments for primary, secondary, and safety outcome data collection**

Variable	Measure
<b>Primary outcome</b>	
Naming ability	Change in Boston Naming Test (BNT) score from baseline (Visit 2) to post-intervention (Visit 4, after 3 weeks of iSLT). The BNT scale is a performance-based measure commonly used to assess the visual confrontation naming ability among adults with aphasia. Participants are shown pictures of common objects and asked to name each stimulus item within 20 seconds. The score range is 0–60; higher scores mean better outcomes in naming ability.
<b>Secondary outcome</b>	
Aphasia quotient	Change in Western Aphasia Battery (WAB) score compared with baseline. The WAB scale is a weighted average of all subtest scores relating to spoken language. It consists of the sum of all subtest scores from the first four parts of the WAB (spontaneous speech, auditory verbal comprehension, repetition, and naming and word finding), recording the total average score and standard deviation. The score range is 0–100; higher scores indicate better performance.

Daily communication	Change in the Communication Activities of Daily Living–Third Edition (CADL-3) compared with baseline. The CADL-3 scale contains 50 items assessing the functional communication skills of adults with neurogenic communication disorders in seven areas. The participants receive a score of 0, 1, or 2 for each item; higher scores reflect better communicative success.
Speech language function assessment	Change in ICF speech language function assessment compared with baseline. The aphasia-adapted ICF speech language function assessment will be used for self-evaluation of communication functions, participation, and activity. The score range is -2 to +2; higher scores mean better outcome in quality of life.
Activities of daily living	Change in Barthel Index (BI) score compared with baseline.
Post-stroke Depression assessment	Change in Stroke Aphasic Depression Questionnaire-hospital version (SADQ-H10) compared with baseline.
<b>Surgical safety outcomes</b>	
Muscle strength	Change in Medical Research Council grading system score compared with baseline.
Spasticity	Change in the Modified Ashworth Scale (MAS) score compared with baseline.
Range of motion	Change in range of motion of the main joints of the upper limbs score compared with baseline.
Sensory function assessment	Change in the tactile sensory threshold and 2-point discrimination score compared with baseline.

### Brain plasticity evaluation

Explorative evaluations included brain functional plasticity detection using functional MRI (fMRI) and EEG. Resting-state, task-designed functional and structural MRI using a GE 3.0 T MRI scanner (MR750) will be collected at baseline, and at V2, V4 and V5 follow-ups. In the task-designed MRI and EEG evaluations, picture naming tasks and semantic prediction tasks will be used to assess patient recovery and the related central plasticity mechanism.



## 256 **Adverse events**

257 Patient safety will be monitored at each study visit. Patients will receive detailed information  
258 regarding who to contact in case of an adverse event. The investigators will record all descriptions  
259 of adverse events during each visit. In this clinical trial, severe adverse events (SAE) will be  
260 considered death, life-threatening severe deterioration of health requiring inpatient hospitalisation  
261 or prolongation of current hospitalisation, and persistent or significant disability/incapacity  
262 requiring intervention to prevent permanent impairment or damage. Patients with SAEs will be  
263 withdrawn from the clinical trial, as it would be unsafe to continue the trial procedure. If an SAE  
264 occurs, investigators will take immediate treatment measures to ensure patient the safety and report  
265 to the institutional review board and relevant competent authorities within 24 h.

## 267 **Data collection and management**

268 Data will be collected using an electronic data-capture (EDC) system. The data administrator will  
269 be responsible for data management and revision. After the data will be checked and the database is  
270 confirmed to be correct, they will be locked and submitted for statistical analysis. The original  
271 functional neuroimaging dataset containing patient-identifying information will be presented as a  
272 disk, while the data anonymised equivalent will be saved and analysed.

## 273 **Analyses**

### 274 **Sample size**

275 As mentioned, the primary outcome of this study will be the change in naming score from baseline  
276 to post-intervention. According to the literature<sup>16 19</sup>, the naming score can be improved after  
277 intensive speech therapy and verified after non-invasive brain stimulation therapy<sup>21 22</sup>. In the pre-  
278 print data, which is a phase-I cohort study<sup>36</sup> including patients with post-stroke aphasia who  
279 received NC7 plus iSLT, the patient naming score evaluated by Boston Naming Test (BNT) was  
280 increased by 11.2 points on average, while that of the patients who received iSLT alone increased

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3 281 by 5.7 points on average from our literature review<sup>37</sup>. According to results of our phase-I study, the  
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6 282 standard deviation was 6.2. With a 2-sided significance level of 0.05, a sample size of 40 patients  
7  
8 283 (20 per group) provided 80% statistical power to demonstrate the difference in the change in BNT  
9  
10 284 scores compared with baseline. Considering a drop-out rate of 20%, 50 patients (25 per group) will  
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12 285 recruit.

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## 287 **Statistical analysis**

288 Analyses of the primary endpoints will be performed on the full analysis set, which will include all  
289 patients randomly allocated to the study treatment. The per-protocol set will include all patients  
290 who will have completed the study without major protocol deviations. Safety will be evaluated in  
291 all patients receiving study treatment and analysed using descriptive statistics.

292 Categorical data will be presented as frequencies and percentages, and continuous data as mean  
293 (standard deviation) or median (interquartile range). Analysis of covariance (ANCOVA) will be  
294 used to conduct between-group comparisons of changes from baseline in primary and secondary  
295 outcomes. The baseline and centre values will be covariates. Generalised estimating equation  
296 models will be used to analyse the longitudinal data between the groups. Subgroup analyses will  
297 include study centre and type, aetiology, and severity of aphasia. Sensitivity analysis will be  
298 performed on missing data for the primary endpoint. All hypothesis tests will be are two-sided, and  
299 statistical significance will be considered at  $P < 0.05$ .

## 301 **ETHICS AND DISSEMINATION**

302 Ethical approval for this trial was granted by the Institutional Review Board of Huashan Hospital,  
303 Fudan University, and by the institutional review boards of all participating institutions  
304 (Supplemental Table 1). All patients will sign informed prior to enrolment. Patients may withdraw  
305 from the study at any time. Important protocol modifications will be communicated to the relevant

1  
2  
3 306 members of the research team. All procedures will be performed in accordance with the principles  
4  
5 307 of the Declaration of Helsinki.  
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## 10 309 **Patient and public involvement**

11  
12 310 We asked patients with post-stroke chronic aphasia in rehabilitation facilities for advice on how to  
13  
14 311 meet their physical and emotional needs. The doctors and therapists from the rehabilitation facilities  
15  
16 312 will provide support for the recruitment process. The study results will be disseminated to the  
17  
18 313 public upon completion of the trial and individual test results will be provided to patients upon  
19  
20 314 request.  
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## 26 316 **DISCUSSION**

27  
28 317 Owing to the high morbidity and heavy disease burden of stroke in China<sup>38</sup>, there is an urgent need  
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30 318 for effective treatments of chronic post-stroke aphasia. This current manuscript describes the  
31  
32 319 methodology of a trial designed to evaluate the effects of NC7 on language-impairment symptoms  
33  
34 320 in patients with chronic post-stroke aphasia. This study bears major importance because it could  
35  
36 321 provide evidence for the validity of a novel therapeutic strategy for improving language function  
37  
38 322 while attenuating stroke-related dysfunctions.  
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41  
42 323 This study focuses on the evaluation of postoperative language function. Language function can be  
43  
44 324 assessed using naming tests and communication ability assessments, for instance. Patients with  
45  
46 325 aphasia who receive iSLT or non-invasive peripheral stimulation can exhibit improvements in  
47  
48 326 naming ability<sup>39</sup> and social communication<sup>17</sup>; however, the effect sizes are usually modest. In a  
49  
50 327 previous study, we found that the naming ability of patients after CC7 significantly improved, and  
51  
52 328 many other researchers have also used the suitable correct spontaneous naming scores as the only  
53  
54 329 BNT-related index for evaluating language function<sup>40 41</sup>. In this study, we will use the BNT scale as  
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56 330 an evaluation index for language function as the primary outcome and the WAB, CADL  
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331 Communication Scale, ADL Scale, and Post-Stroke Depression Scale scores as secondary  
332 indicators of language repetition, listening comprehension, communication ability, daily life, and  
333 psychological status. The ICF speech and language function assessment can detect the degree of  
334 changes in voice intonation, oral motor ability, articulation intelligibility, and oral expression to  
335 exclude the possible reduction of spasticity after neurotomy for the interference with study results.

336 CC7 was first invented by Gu et al.<sup>42-44</sup> to treat limb dysfunction after brachial plexus injury, and  
337 the follow-up work showed neuroplastic changes between the hemispheres after surgery<sup>45 46</sup>. Based  
338 on this theoretical perspective, Xu originally proposed the scientific viewpoint that “One  
339 hemisphere controls both limbs” and expanded the development of the “contralateral C7 nerve  
340 transfer” to “contralateral C7 to C7 cross nerve transfer” for treating central hemiplegia<sup>24 47 48</sup>. Our  
341 previous investigations suggested the possible correlation between CC7 and the improvement of  
342 chronic aphasia, an effect occurring in the early postoperative period<sup>36</sup>. Thus, the possibility of  
343 aphasia recovery through NC7 at the intervertebral foramen caught our attention. In this study, we  
344 measured the muscle strength, joint range of motion, upper limb MAS score, and sensory  
345 assessment as safety indicators to evaluate the effects of NC7 on the right side. If NC7 does  
346 improve language function without physical dysfunction, it will provide an entirely novel  
347 perspective for the treatment of chronic post-stroke aphasia. However, the mechanisms underlying  
348 NC7 efficacy in chronic aphasia are not fully understood. We believe that this clinical improvement  
349 in language function is related to NC7 stimulating neuroplasticity. This requires more objective  
350 functional imaging evidence. Several recent studies have reviewed the mechanisms of underlying  
351 the recovery from aphasia. In some cases, the therapy mechanisms<sup>49 50</sup> are evidenced by changes in  
352 task-related brain activations or changes in functional connectivity within functional networks<sup>51 52</sup>.

353 Here, we will use fMRI and EEG methods in relation to naming ability and semantic prediction to  
354 investigate the neural and physiological states induced by changes in language function after NC7.

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3 355 In conclusion, this will be the first RCT to evaluate the effect of surgery in patients with chronic  
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6 356 post-stroke aphasia for whom no effective treatment is available. If found to be efficient, this  
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8 357 strategy can be implemented regularly because of its ease of application and low cost. Moreover,  
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10 358 larger trials should be extended to other diseases with central nerve injuries to assess the positive  
11  
12 359 effects of this strategy on language and other functions. Once our hypothesis is confirmed, this trial  
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14  
15 360 will provide important evidence to support the use of NC7 at the intervertebral foramen as a novel  
16  
17 361 treatment approach for chronic aphasia. A limitation of this study is that it is not double-blind but  
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19 362 evaluator-blind, and the experimental group may experience a minor placebo effect. Nevertheless, a  
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22 363 secondary endpoint assessment at 6 months post-intervention is scheduled to be conducted to offset  
23  
24 364 the short-term post-surgery placebo effect. At that time, the patient's placebo effect due to invasive  
25  
26 365 interventions will be greatly reduced.  
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28  
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### 31 367 **Abbreviations list**

32  
33  
34 368 RCT = randomised controlled trials; CC7 = contralateral C7 to C7 cross nerve transfer; NC7 = C7  
35  
36 369 neurotomy; iSLT = intensive speech and language therapy; DRG=dorsal root ganglion; BDAE=  
37  
38 370 Boston Diagnostic Aphasia Examination; BNT = Boston naming test; WAB = Western Aphasia  
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40  
41 371 Battery; CADL = Communication Activities of Daily Living; ADL= Activity of Daily Living;  
42  
43 372 ICF=International classification of Functioning, Disability and Health; SADQ-H10= Stroke  
44  
45 373 Aphasic Depression Questionnaire-hospital version; EEG = Electroencephalogram; fMRI =  
46  
47  
48 374 functional magnetic resonance imaging; SAE = Severe Adverse Events.  
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### 52 376 **Competing Interests**

53  
54 377 None declared.  
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### 59 379 **Patient consent for publication**

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3 380 Not required.  
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6 381  
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13  
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18  
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## 33 393 **Contributors**

34 394 WX is the principal investigator of this study and refined the protocol. TL and JF wrote the  
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36  
37 395 manuscript and contributed to the design of the study. ML, the medical statistician for the study,  
38  
39 396 contributed to the statistical design and ethical approval. WC contributed to brain plasticity  
40  
41 397 evaluation design and guidance. YG participated in the concept and design of the study. RH, XM,  
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43  
44 398 WQ, YZ, XC, LD have revised the protocol critically for multicentre intellectual content. All  
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46 399 authors read and approved the final manuscript.  
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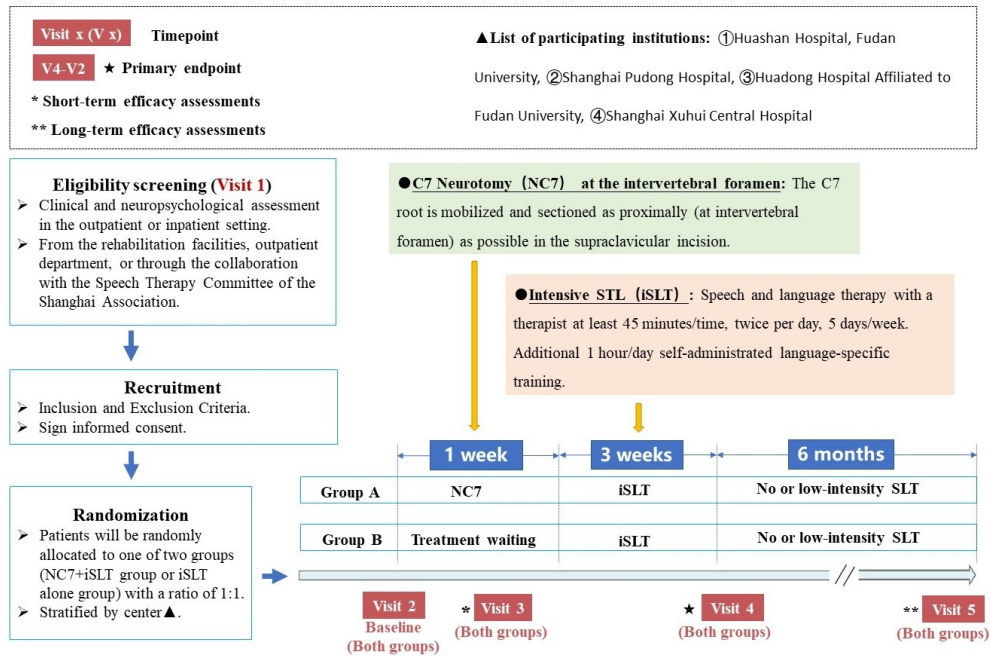
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54 522 **Figure caption**55  
56 523 **Figure 1.** Trial design in detail and patient flow chart.  
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Trial design in detail and patient flow chart.

351x234mm (96 x 96 DPI)

**Supplemental Table 1. List of all participating institutions and institutional review boards in this trial**

<b>Major research institution</b>	<b>Name of institutional review board</b>
Huashan Hospital, Fudan University	Institutional Review Board of Huashan Hospital Affiliated to Fudan University
<b>Sub-centre research institution</b>	<b>Name of institutional review board</b>
Shanghai Pudong Hospital	Academic Ethics Committee of Shanghai Pudong Hospital
Huadong Hospital Affiliated to Fudan University	Ethics Committee of Huadong Hospital Affiliated to Fudan University
Shanghai Xuhui Central Hospital	Shanghai Xuhui Central Hospital Ethics Committee



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

Section/item	Item No	Description	Addressed on page number
<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 _____
	2b	All items from the World Health Organization Trial Registration Data Set	_____ NA _____
Protocol version	3	Date and version identifier	_____ 1-2 _____
Funding	4	Sources and types of financial, material, and other support	_____ 17 _____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____ 1,17 _____
	5b	Name and contact information for the trial sponsor	_____ NA _____
	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	_____ NA _____
	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)	_____ 5-7, 13-14 _____

1	<b>Introduction</b>			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	_____ 3-5 _____
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	_____ 3-5 _____
7				
8	Objectives	7	Specific objectives or hypotheses	_____ 5 _____
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____ 5, 6 _____
12				
13				
14	<b>Methods: Participants, interventions, and outcomes</b>			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	_____ 7,8 _____
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	_____ 6-8 _____
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	_____ 7-9 _____
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	_____ 12 _____
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	_____ NA _____
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____ 7-9 _____
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	_____ 9-12 _____
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	_____ 8,9 _____
39			participants. A schematic diagram is highly recommended (see Figure)	
40				
41				
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____ 12,13 _____
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____ 5-7 _____
5				

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

#### 7 Allocation:

8				
9				
10	Sequence	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____ 9-10 _____
11	generation			
12				
13				
14				
15				
16	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____ 7-10 _____
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____ NA _____
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____ 9 _____
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____ NA _____
28				
29				
30				

### 31 **Methods: Data collection, management, and analysis**

32				
33	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____ 12,13 _____
34	methods			
35				
36				
37				
38				
39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____ NA _____
40				
41				
42				

1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____12_____
2				
3				
4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____13_____
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____13_____
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____NA_____
11				
12				
13				
14	<b>Methods: Monitoring</b>			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____NA_____
17				
18				
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____NA_____
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____12_____
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____NA_____
29				
30				
31				
32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____13,14_____
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____NA_____
38				
39				
40				
41				
42				



1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____ NA ____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____ NA ____
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____ NA ____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____ 16,17 ____
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____ 12 ____
14				
15				
16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____ NA ____
17				
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____ 14 ____
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	____ NA ____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____ NA ____
27				
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Supplemental Material__
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____ NA ____
35				
36				

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