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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065173
Article Type:	Protocol
Date Submitted by the Author:	30-May-2022
Complete List of Authors:	Li, Tie; Huashan Hospital Fudan University Department of Hand Surgery Feng, Juntao; Huashan Hospital Fudan University Department of Hand Surgery Hu, Ruiping; Huashan Hospital Fudan University, Department of Rehabilitation Lv, Minzhi; Fudan University, Center of Evidence-Based Medicine, Department of Biostatistics, School of Public Health Chang, Wenshuo; Shanghai International Studies University, Institute of Linguistics Ma, Xingyi; Huashan Hospital Fudan University, Handsurgery Qi, Wenjun; Huashan Hospital Fudan University Zhang, Ying; Shanghai Xuhui Central Hospital, Department of Rehabilitation Chen, Xiuen; Huadong Hospital Affiliated to Fudan University, Department of Rehabilitation Ding, Ling; Shanghai Pudong Hospital, Department of Rehabilitation Gu, Yudong; Huashan Hospital Fudan University Department of Hand Surgery Xu, Wendong; Huashan Hospital Fudan University, Handsurgery
Keywords:	Stroke < NEUROLOGY, Neurosurgery < SURGERY, Clinical trials < THERAPEUTICS

TITLE PAGE

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

Authors:

Tie Li[1-3,7-10†], Juntao Feng[1-3,7-10†], Ruiping Hu[4], Minzhi Lv[6],Wenshuo Chang[5], Xingyi Ma[1,2], Wenjun Qi[1,2], Ying Zhang[11], Xiuen Chen[12], Ling Ding[13], Yudong Gu[1-3,7-10], Wendong Xu[1-3,7-10*]

[1] Department of Hand Surgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China.
[2] Department of Hand and Upper Extremity Surgery, Limb Function Reconstruction Center, Jing'an District Central Hospital, Shanghai, China.
[3] National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University.
[4] Department of Rehabilitation, Huashan Hospital, Shanghai Medical College, Fudan University Shanghai, China.
[5] Institute of Linguistics, Shanghai International Studies University, Shanghai, China.
[6] Center of Evidence-Based Medicine, Department of Biostatistics, School of Public Health, Fudan University, Shanghai, China.
[7] Key Laboratory of Hand Reconstruction, Ministry of Health, Shanghai, China.
[8] Shanghai Key Laboratory of Peripheral Nerve and Microsurgery, Shanghai, China.
[9] State Key Laboratory of Medical Neurobiology, Fudan University, Shanghai, China.
[10] Shanghai Engineering Research Center of Artificial Intelligence Medical Auxiliary Equipment.
[11] Department of Rehabilitation, Shanghai Xuhui District Central Hospital, Shanghai, China.
[12] Department of Rehabilitation, Huadong Hospital Affiliated to Fudan University, Shanghai, China.
[13] Department of Rehabilitation, Shanghai Pudong Hospital, Shanghai, China.

†These authors have contributed equally to this work and share first authorship.

***Corresponding Author:**
Prof. Wendong Xu
Email: wendongxu@fudan.edu.cn
Postal address: Department of Handsurgery, Huashan Hospital, Fudan University; No.12 Middle Wulumuqi Rd., Shanghai, China.

Keywords: chronic aphasia after stroke, neurotomy of C7 nerve at intervertebral foramen (NC7), intensive speech and language therapy (iSLT), neuroplasticity

Word count: 3,875

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≥ 12 months, aphasia quotient of WAB score ≤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

ARTICLE SUMMARY

Strengths and limitations of this study

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

INTRODUCTION

Background and rationale

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

Language is an indispensable part of cognitive function, and affects patients' attention, comprehension and other functions[9]. Aphasia, impairment of language after stroke or other neurological insult, is a common and often devastating condition that affects nearly every social activity and interaction. The language function of the patients will recover spontaneously to varying degrees [10]. The traditional view is that language function will reach the chronic phase at 6-9 months after stroke, and with few changes later[11 12]. 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"[13], although this "recovered" may also have mild residual impairment that could be detected by a more sensitive assessment[14]. However, some forms of aphasia persists into the chronic phase in half of patients at least[15].

Although most aphasia therapy studies have enrolled chronic patients, it seems likely that earlier aphasia therapy is also effective, which has achieved good results in improving aphasia after stroke[16]. Common aphasia rehabilitation treatments include classic speech-language rehabilitation training, as well as low-frequency electrical stimulation therapy, repetitive transcranial magnetic stimulation and transcranial direct current stimulation. A large number of clinical studies[17 18] have

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

We previously developed a surgical procedure for contralateral seventh cervical nerve transfer from the nonparalyzed side to the paralyzed side(contralateral C7 to C7 cross nerve transfer, CC7), after which patients demonstrated improved motor function and reduced spasticity in the paralyzed arm over 12 months[25]. So far more than 1,000 patients have undergone the surgery[26], in addition to arm motor recovery, the improvement of language was frequently self-reported by patients and caregivers during the following-up process, and it would occur very rapidly after CC7 treatment. A few days is far from enough time for the transferred C7 nerve to regenerate[27], thus we assumed that the rapid improvement of language function was mediated by the neurotomy C7 nerve on the

paralyzed side (right side), rather than nerve regeneration. During the CC7 operation[28], to make the C7 nerve on the paralyzed side provide more length of nerve fibres, we cut the C7 nerve root at intervertebral foramen. Based on anatomical research, the anterior and posterior roots converge into spinal nerves at the intervertebral foramen, and the posterior roots enlarge near the intervertebral foramen to form ganglia, also known as dorsal root ganglion (DRG)[29 30]. The exact location of neurotomy is at the transitional junction of the C7 nerve root with DRG [31]. In most cases, aphasia is caused by strokes involving the left hemisphere, with more extensive damage typically being associated with more severe aphasia.[32] Based on the anatomy of brain functional areas, since the motor centre is adjacent to the language centre, if the motor centre can be changed artificially, it's possible to induce the language centre and produce related functional changes. Human C7 nerve contains 80,000 fibers[33], 94% of which are sensory fibres emitted by DRG[34]. Hence, the neurotomy of C7 nerve root with DRG can block the sensory ascending pathway from the affected limb to the brain. Therefore, we speculate that the clinical phenomenon of language function improvement is due to the stimulation inducing neuroplasticity of the "language centre", that is, "Reconstructing the peripheral nerve changes the central nervous system." To confirm our hypothesis, we designed this trial to evaluate the surgical effect of neurotomy of C7 nerve at intervertebral foramen (NC7) on underlying neuroplasticity in patients with chronic aphasia after stroke. Meanwhile, the iSLT is selected as the intervention method of control group, and will evaluate the effect of intensive intervention after 3 weeks and the maintenance effect after 6 months of the both groups respectively.

Aims of the study

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

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

plus intensive speech and language therapy (3 weeks) and intensive speech and language therapy (3 weeks) alone, and the further validation of the safety and long-term (6 months) effectiveness of NC7 surgical programme. (2) to evaluate the motor and sensorimotor function of paralyzed arm, clarify the correlation between motor function and language function changes, postoperatively. (3) to confirm the central mechanism of neurotomy of C7 nerve at intervertebral foramen and access the underlying neuroplasticity via functional neuroimaging measurements.

METHODS/DESIGN

Trial design

This study is a multicenter, randomized controlled trial with two parallel groups and 6-month follow-up. Based on language and motor function analysis, the protocol that compares patients with chronic aphasia treated with the neurotomy of C7 nerve at intervertebral foramen (NC7) and intensive speech and language therapy (iSLT) (Group A), with a control group participating in iSLT alone (Group B). The participants involved will be randomly allocated to one of two groups (NC7+iSLT group or iSLT group) with a ratio of 1:1. The study is conducted in collaboration of the Speech Therapy Committee of Shanghai Association of Rehabilitation Medicine (STCSARM), and the participants will be collected from rehabilitation facilities of this organization. Ethical approval for this trial was granted by the Institutional Review Board of Huashan Hospital, Fudan University (HIRB), and by the IRBs of the all participating facilities. Patients who will receive an indication for outpatient rehabilitation treatment at any of four centres, based on the eligibility criteria listed below. The potentially eligible patients will be invited to participate via a text message after signing the informed consent.

Eligibility criteria

Inclusion criteria:

1) Aphasia for over 12 months after single onset of infarction or hemorrhage of the left hemisphere

which is confirmed by magnetic resonance imaging;

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

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

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

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

6) The subjects can fully understand and agree with the doctor's treatment plan and sign the informed consent.

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

Exclusion criteria:

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

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

3) Suffering from serious, untreated mental illness;

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

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

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

7) Severe motor speech disorder and hearing impairment;

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

Interventions

Neurotomy of C7 nerve at intervertebral foramen

Make a 6-cm long longitudinal incision along the medial border of the sternocleidomastoid muscle on right side after cervical plexus anesthesia/general anesthesia (depend on patient preference and through risk assessment by anesthesiologist), carefully separate the structure layer by layer and identify the brachial plexus by marking the C7 nerve with a vessel loop. The C7 root is mobilized and sectioned as proximally (at intervertebral foramen) as possible. Considering that some patients have limb hemiplegia, CC7 surgery may be required to improve limb function at the end of this

trial. Therefore, we fixed the severed C7 root to the fascia at the junction of the scapulohyoid and sternocleidomastoid muscles with silk thread, making it easier to find and then anastomosed with the contralateral C7 root during the later CC7[28] surgical programme.

iSLT Rehabilitation

With reference to the previous studies, we formulated a 3-week iSLT plan. Speech and language therapy with a therapist at least 45 minutes/time, twice per day, 5 days/week. Additional 1 hour/day self-administrated language-specific training. For arm motor, the rehabilitation therapy based on the Brunnstrom principle is provided. Rehabilitation includes active exercise, passive range of motion training, occupational therapy, functional training, physical therapy, acupuncture, massage and the use of orthotics. Patients receive rehabilitation treatment at different study centres, where qualified rehabilitation therapists perform the therapy.

Study setting

A total of 50 patients with diagnosed aphasia with hemiplegia after chronic stroke will be recruited. Patients will receive hospitalized treatment over a period of 3-4 weeks in the research institutions, with follow-up assessment at 6 months after start of treatment (Figure1). On their first visit, patients will be selected for study eligibility according to the inclusion and exclusion criteria. After this baseline evaluation, eligible patients will be randomly assigned to one of the two groups according to different centres. Patients of Group A receive NC7 immediately after assignment, and receive short-term efficacy assessment after 3 days, the total perioperative period is one week. In the meantime, patients of Group B are waiting for therapy programme. Then, the iSLT and upper extremity motor rehabilitation programme are provided for patients in both groups. After a 3-week inpatient invention, all the patients received primary endpoint assessments, then they continue to receive conventional low-intensity SLT at home or in other centres. For arm motor, patients are

guided to consistently keep the rehabilitation, and the therapy intensity and duration are recorded by the therapist or caregiver. Six months later, the second visit, all the patients will receive interim evaluation by trained therapist belonging to an independent team. Afterwards, the NC7 and postoperative rehabilitation programme (both of iSLT and motor rehabilitation) which is consistent with Group A are performed in patients of Group B. Likewise, these patients will receive a short-term and long-term follow-up for efficacy assessment. Schedule of enrolment, interventions 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.

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

Primary outcomes			√		√*		√★		√**
Secondary outcomes			√		√*		√★		√**
Brain plasticity evaluation			√				√★		√**
Safety outcomes			√		√*		√★		√**
Adverse event assessment					√		√		√

(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

Chinese version of BNT[35 36].

The secondary outcomes include Aphasia quotient, daily communication (CADL-3), activities of daily living (Barthel Index), speech language function assessment (ICF[37] speech language function assessment), post stroke depression assessment (Hamilton Rating Scale for Depression, HRSD) and safety outcomes in different groups. Assessments performed to collect data for the primary, secondary, and safety outcomes are listed in the Table 2.

Table 2. Assessments performed to collect data for the primary, secondary, and safety outcomes

Variable	Measure
Primary outcome	
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.
Secondary outcome	
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

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

Data collection and management

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

Analyses

Sample size

This study intends to use the change of naming score from baseline to post-intervention as the primary outcome. According to literature[17 20], the naming score can be improved after intensive speech therapy, and also can be verified after non-invasive brain stimulation therapy[22 23]. Combined with our previous data, it is assumed that postoperative (NC7) + rehabilitation (iSLT) can improve the naming ability with an average score of 2.04 ± 1.03 points. While the iSLT alone group can improve the naming ability with an average score of 0.7 ± 0.24 points. With the power of 90% and the 5% significant level(two-sided), the sample size of each group was 21. With loss to follow-up rate is 15%, the total maximum sample size was 50 cases.

Statistical analysis

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

Categorical data were described as frequency and percentage, and continuous data were described by mean (standard deviation) or median (interquantile range). Between-group comparisons of

changes from baseline in primary and secondary outcome were performed using analysis of covariance (ANCOVA). The baseline value and centre are covariates. Generalized estimating equation (GEE) models were used to analysis the longitudinal data between groups. Subgroup Analysis includes study centre, type of aphasia, etiology of aphasia, and severity of aphasia. Sensitivity analysis was performed on missing data for the primary endpoint. All hypothesis tests are two-sided, and values of $P<0.05$ is considered statistical significant.

Ethics and dissemination

The study has been approved by the Institutional Review Board of Huashan Hospital, Fudan University (No. KY2021-592). All patients will write informed consent prior to entry to the study. Patients may withdraw from the study at any time. Important protocol modifications will be communicated to the relevant members of the research team. The procedure will be performed following the principles described in the declaration of Helsinki.

Patient and public involvement

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

DISCUSSION

Due to the high morbidity and heavy diseases burden of stroke in China[38], the effective treatments of chronic aphasia after stroke are in urgent need. The current article describes the methodology of a trial design for the effects of NC7 on symptom of language impairment in patients with chronic

aphasia after stroke. This study bears major importance because it could potentially provide evidence for the validity of a novel therapy strategy improving language function while diminishing the disfunctions after stroke.

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

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

of motion, upper limb MAS score and sensory assessment as safety indicators to evaluate the effect of the NC7 on the right side. If the NC7 does improve language function with no physical dysfunction, it will provide an entirely novel perspective for the treatment of chronic aphasia after stroke. However, the mechanisms by which NC7 are thought to be effective in chronic aphasia but not fully understood. We consider that this clinical phenomenon of language function improvement is due to stimulate the neuroplasticity by NC7. This requires more objective functional imaging evidence to confirm. Several recent publications have reviewed the mechanisms of aphasia recovery, and in some cases the mechanisms of therapy[48 49] revealed by changes in task-related brain activations or changes in functional connectivity within functional networks[50 51]. Here, we use fMRI and EEG methods to observe around the naming ability and semantic prediction, to investigate the neural and physiological states induced by changes in language function after NC7.

In conclusion, this is the first RCT to evaluate the surgical effect in patients with chronic aphasia after stroke for whom no effective treatment is available. If found to be efficient, this strategy could be regularly implemented, as it is easily applicable and low-cost. Moreover, larger trials could be extended to other central nerve injury diseases to check for efficiency in language and other functions. Once our hypothesis is confirmed, this trial will provide important evidence for supporting neurotomy of C7 nerve at intervertebral foramen as a treatment approach for chronic aphasia, which may provide a novel perspective on aphasia treatment and the interaction with peripheral between central nervous system.

Abbreviations

RCT = randomized controlled trials; CC7 = contralateral C7 to C7 cross nerve transfer; NC7 = neurotomy of C7 nerve at intervertebral foramen; iSLT = intensive speech and language therapy; DRG=dorsal root ganglion; IRB = Institutional Review Board; BDAE= Boston Diagnostic Aphasia Examination; BNT = Boston naming test; WAB = Western Aphasia Battery; CADL =

Communication Activities of Daily Living; ADL= Activity of Daily Living; ICF=International classification of Functioning, Disability and Health; HRSD= Hamilton Rating Scale for Depression , EEG = Electroencephalography; fMRI = functional magnetic resonance imaging; SAE = Severe Adverse Events.

Declarations

The authors declare that they have no competing interests.

Patient consent for publication

Not required.

Funding

This protocol was funded by the National Natural Science Foundation of China (82021002, 81830063); CAMS Innovation Fund for Medical Sciences (2019-I2M-5-007) and Special Project of Clinical and Translational Medicine research cultivating program(2021-I2M-C&T-B-100); Shanghai Clinical Research Center for Aging and Medicine (19MC1910500); 2021 pilot project of clinical medical research，Shanghai Medical College; Fudan University.

Acknowledgements

We would like to thank the study participants, our colleagues at Huashan Hospital, Fudan University and all the participating institutions.

Contributors

WD-X is the principal investigator of this study and refined the protocol. TL and JT-F wrote the manuscript and contributed to the design of the study. MZ-L, the medical statistician for the study,

contributed to the statistical design and ethical approval. WS-C contributed to brain plasticity evaluation design and guidance. YD-G participated in the concept and design of the study. RP-H, XY-M, QJ-Q, YL, XE-C, LD have revised the protocol critically for multicentre intellectual content. All authors read and approved the final manuscript.

REFERENCES

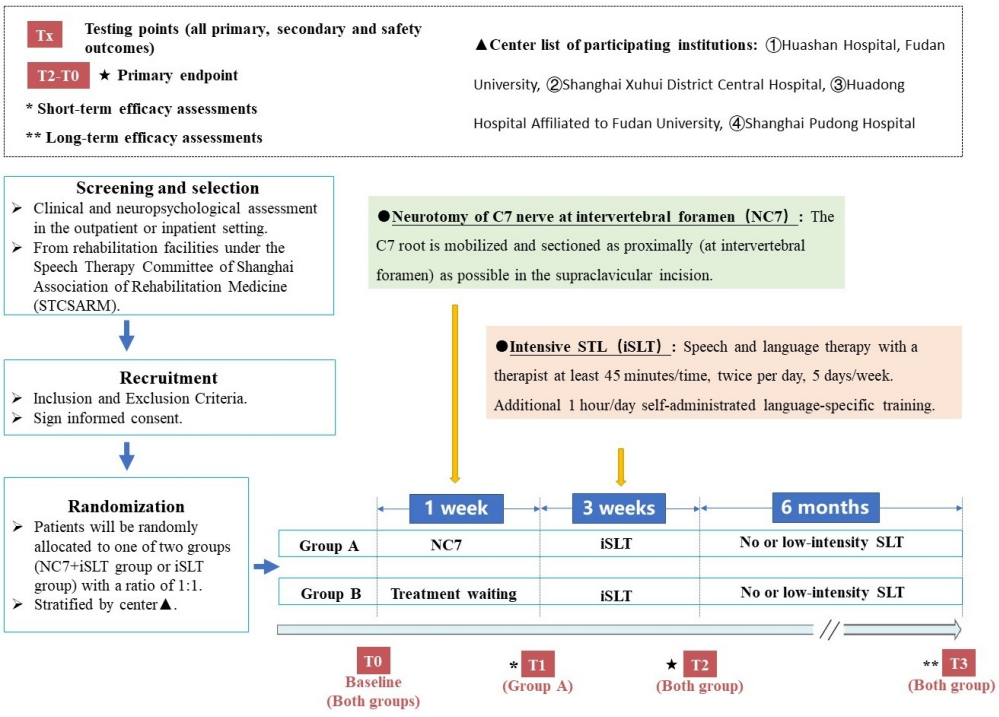
1. Stefaniak JD, Halai AD, Lambon Ralph MA. The neural and neurocomputational bases of recovery from post-stroke aphasia. *Nat Rev Neurol* 2020;**16**(1):43-55.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017;**135**(10):e146-e603.
3. Engelter ST, Gostynski M, Papa S, et al. Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis. *Stroke; a journal of cerebral circulation* 2006;**37**(6):1379-84.
4. Hilari K. The impact of stroke: are people with aphasia different to those without? *Disability and rehabilitation* 2011;**33**(3):211-8.
5. Pollock A, St George B, Fenton M, et al. Top ten research priorities relating to life after stroke. *The Lancet Neurology* 2012;**11**(3):209.
6. Flowers HL, Skoretz SA, Silver FL, et al. Poststroke Aphasia Frequency, Recovery, and Outcomes: A Systematic Review and Meta-Analysis. *Archives of physical medicine and rehabilitation* 2016;**97**(12):2188-201.e8.
7. Bonilha HS, Simpson AN, Ellis C, et al. The one-year attributable cost of post-stroke dysphagia. *Dysphagia* 2014;**29**(5):545-52.
8. Doucet T, Muller F, Verdun-Esquer C, et al. Returning to work after a stroke: a retrospective study at the Physical and Rehabilitation Medicine Center La Tour de Gassies. *Annals of physical and rehabilitation medicine* 2012;**55**(2):112-27.
9. Murray LL. Attention and other cognitive deficits in aphasia: presence and relation to language and communication measures. *American journal of speech-language pathology* 2012;**21**(2):S51-64.
10. Yagata SA, Yen M, McCarron A, et al. Rapid recovery from aphasia after infarction of Wernicke's area. *Aphasiology* 2017;**31**(8):951-80.
11. Elkana O, Frost R, Kramer U, et al. Cerebral language reorganization in the chronic stage of recovery: a longitudinal fMRI study. *Cortex; a journal devoted to the study of the nervous system and behavior* 2013;**49**(1):71-81.
12. Pedersen PM, Jørgensen HS, Nakayama H, et al. Aphasia in acute stroke: incidence, determinants, and recovery. *Ann Neurol* 1995;**38**(4):659-66.
13. Laska AC, Hellblom A, Murray V, et al. Aphasia in acute stroke and relation to outcome. *Journal of internal medicine* 2001;**249**(5):413-22.
14. El Hachioui H, Visch-Brink EG, de Lau LM, et al. Screening tests for aphasia in patients with stroke: a systematic review. *Journal of neurology* 2017;**264**(2):211-20.
15. Wade DT, Hewer RL, David RM, et al. Aphasia after stroke: natural history and associated deficits. *J Neurol Neurosurg Psychiatry* 1986;**49**(1):11-6.
16. Fridriksson J, Hillis AE. Current Approaches to the Treatment of Post-Stroke Aphasia. *J Stroke* 2021;**23**(2):183-201.
17. Brady MC, Kelly H, Godwin J, et al. Speech and language therapy for aphasia following stroke. *The Cochrane database of systematic reviews* 2016;**2016**(6):Cd000425.

18. Breitenstein C, Grewe T, Flöel A, et al. Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *Lancet (London, England)* 2017;**389**(10078):1528-38.
19. Doppelbauer L, Mohr B, Dreyer FR, et al. Long-Term Stability of Short-Term Intensive Language-Action Therapy in Chronic Aphasia: A 1-2 year Follow-Up Study. *Neurorehabilitation and neural repair* 2021;**35**(10):861-70.
20. Stahl B, Mohr B, Büscher V, et al. Efficacy of intensive aphasia therapy in patients with chronic stroke: a randomised controlled trial. *J Neurol Neurosurg Psychiatry* 2018;**89**(6):586-92.
21. Elsner B, Kugler J, Pohl M, et al. Transcranial direct current stimulation (tDCS) for improving aphasia in adults with aphasia after stroke. *The Cochrane database of systematic reviews* 2019;**5**(5):Cd009760.
22. Fridriksson J, Rorden C, Elm J, et al. Transcranial Direct Current Stimulation vs Sham Stimulation to Treat Aphasia After Stroke: A Randomized Clinical Trial. *JAMA neurology* 2018;**75**(12):1470-76.
23. Meinzer M, Darkow R, Lindenberg R, et al. Electrical stimulation of the motor cortex enhances treatment outcome in post-stroke aphasia. *Brain : a journal of neurology* 2016;**139**(Pt 4):1152-63.
24. Heikkinen PH, Pulvermüller F, Mäkelä JP, et al. Combining rTMS With Intensive Language-Action Therapy in Chronic Aphasia: A Randomized Controlled Trial. *Frontiers in neuroscience* 2018;**12**:1036.
25. Zheng MX, Hua XY, Feng JT, et al. Trial of Contralateral Seventh Cervical Nerve Transfer for Spastic Arm Paralysis. *The New England journal of medicine* 2018;**378**(1):22-34.
26. Feng J, Li T, Lv M, et al. Reconstruction of paralyzed arm function in patients with hemiplegia through contralateral seventh cervical nerve cross transfer: a multicenter study and real-world practice guidance. *EClinicalMedicine* 2022;**43**:101258.
27. Maas MB, Lev MH, Ay H, et al. The prognosis for aphasia in stroke. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 2012;**21**(5):350-7.
28. Xu WD. Surgical Technique of Xu's CC7 Procedure "Contralateral C7 to C7 Cross Nerve Transfer Through a Trans Longus Colli, Prespinal Route for Treating Spastic Arm". *Operative neurosurgery (Hagerstown, Md)* 2020;**20**(1):61-68.
29. Takahashi K, Ninomiya T. Morphological changes of dorsal root ganglion cells in the process-forming period. *Prog Neurobiol* 1987;**29**(4):393-410.
30. Leijnse JN, D'Herde K. Revisiting the segmental organization of the human spinal cord. *Journal of anatomy* 2016;**229**(3):384-93.
31. Zhong LY, Wang AP, Hong L, et al. Microanatomy of the brachial plexus roots and its clinical significance. *Surgical and radiologic anatomy : SRA* 2017;**39**(6):601-10.
32. Fridriksson J, den Ouden DB, Hillis AE, et al. Anatomy of aphasia revisited. *Brain : a journal of neurology* 2018;**141**(3):848-62.
33. Gesslbauer B, Hruby LA, Roche AD, et al. Axonal components of nerves innervating the human arm. *Ann Neurol* 2017;**82**(3):396-408.
34. Mille-Hamard L, Bauchet L, Baillet-Derbin C, et al. Estimation of the number and size of female adult rat C4, C5 and C6 dorsal root ganglia (DRG) neurons. *Somatosensory & motor research* 1999;**16**(3):223-8.
35. Cheung RW, Cheung MC, Chan AS. Confrontation naming in Chinese patients with left, right or bilateral brain damage. *Journal of the International Neuropsychological Society : JINS* 2004;**10**(1):46-53.
36. Chen TB, Lin CY, Lin KN, et al. Culture qualitatively but not quantitatively influences performance in the Boston naming test in a chinese-speaking population. *Dementia and geriatric cognitive disorders extra* 2014;**4**(1):86-94.

37. Pike C, Kritzinger A, Pillay B. Social participation in working-age adults with aphasia: an updated systematic review. *Topics in stroke rehabilitation* 2017;**24**(8):627-39.
38. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet (London, England)* 2019;**394**(10204):1145-58.
39. Rossi A, Burkhart C, Dell-Kuster S, et al. Serum anticholinergic activity and postoperative cognitive dysfunction in elderly patients. *Anesthesia and analgesia* 2014;**119**(4):947-55.
40. Nousia A, Siokas V, Aretouli E, et al. Beneficial Effect of Multidomain Cognitive Training on the Neuropsychological Performance of Patients with Early-Stage Alzheimer's Disease. *Neural plasticity* 2018;**2018**:2845176.
41. Gu YD, Zhang GM, Chen DS, et al. Seventh cervical nerve root transfer from the contralateral healthy side for treatment of brachial plexus root avulsion. *Journal of hand surgery (Edinburgh, Scotland)* 1992;**17**(5):518-21.
42. Gu Y, Xu J, Chen L, et al. Long term outcome of contralateral C7 transfer: a report of 32 cases. *Chinese medical journal* 2002;**115**(6):866-8.
43. Gu YD. Contralateral C7 root transfer over the last 20 years in China. *Chinese medical journal* 2007;**120**(13):1123-6.
44. Hua XY, Liu B, Qiu YQ, et al. Long-term ongoing cortical remodeling after contralateral C-7 nerve transfer. *Journal of neurosurgery* 2013;**118**(4):725-9.
45. Jiang S, Li ZY, Hua XY, et al. Reorganization in motor cortex after brachial plexus avulsion injury and repair with the contralateral C7 root transfer in rats. *Microsurgery* 2010;**30**(4):314-20.
46. Xu WD, Hua XY, Zheng MX, et al. Contralateral C7 nerve root transfer in treatment of cerebral palsy in a child: case report. *Microsurgery* 2011;**31**(5):404-8.
47. Hua XY, Qiu YQ, Li T, et al. Contralateral peripheral neurotization for hemiplegic upper extremity after central neurologic injury. *Neurosurgery* 2015;**76**(2):187-95; discussion 95.
48. Nardo D, Holland R, Leff AP, et al. Less is more: neural mechanisms underlying anomia treatment in chronic aphasic patients. *Brain : a journal of neurology* 2017;**140**(11):3039-54.
49. Crinion JT, Leff AP. Using functional imaging to understand therapeutic effects in poststroke aphasia. *Current opinion in neurology* 2015;**28**(4):330-7.
50. Kiran S, Meier EL, Johnson JP. Neuroplasticity in Aphasia: A Proposed Framework of Language Recovery. *Journal of speech, language, and hearing research : JSLHR* 2019;**62**(11):3973-85.
51. Hartwigsen G, Saur D. Neuroimaging of stroke recovery from aphasia - Insights into plasticity of the human language network. *Neuroimage* 2019;**190**:14-31.

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)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____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___

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	6, 7
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9,10
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8,9
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8,9
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
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

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9-10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
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	11
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	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
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	14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-15
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____NA_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
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_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____18____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____14_____
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_____
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_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____NA_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_additional files__
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_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065173.R1
Article Type:	Protocol
Date Submitted by the Author:	30-Dec-2022
Complete List of Authors:	Li, Tie; Huashan Hospital Fudan University Department of Hand Surgery Feng, Juntao; Huashan Hospital Fudan University Department of Hand Surgery Hu, Ruiping; Huashan Hospital Fudan University, Department of Rehabilitation Lv, Minzhi; Fudan University, Center of Evidence-Based Medicine, Department of Biostatistics, School of Public Health Chang, Wenshuo; Shanghai International Studies University, Institute of Linguistics Ma, Xingyi; Huashan Hospital Fudan University, Handsurgery Qi, Wenjun; Huashan Hospital Fudan University Zhang, Ying; Shanghai Xuhui Central Hospital, Department of Rehabilitation Chen, Xiuen; Huadong Hospital Affiliated to Fudan University, Department of Rehabilitation Ding, Ling; Shanghai Pudong Hospital, Department of Rehabilitation Gu, Yudong; Huashan Hospital Fudan University Department of Hand Surgery Xu, Wendong; Huashan Hospital Fudan University, Handsurgery
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Surgery
Keywords:	Stroke < NEUROLOGY, Neurosurgery < SURGERY, Clinical trials < THERAPEUTICS

TITLE PAGE

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

Authors:

Tie Li[1-3,7-10†], Juntao Feng[1-3,7-10†], Ruiping Hu[4], Minzhi Lv[6], Wenshuo Chang[5], Xingyi Ma[1,2], Wenjun Qi[1,2], Ying Zhang[11], Xiuen Chen[12], Ling Ding[13], Yudong Gu[1-3,7-10], Wendong Xu[1-3,7-10*]

[1] Department of Hand Surgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China.
[2] Department of Hand and Upper Extremity Surgery, Limb Function Reconstruction Center, Jing'an District Central Hospital, Shanghai, China.
[3] National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University.
[4] Department of Rehabilitation, Huashan Hospital, Shanghai Medical College, Fudan University Shanghai, China.
[5] Institute of Linguistics, Shanghai International Studies University, Shanghai, China.
[6] Center of Evidence-Based Medicine, Department of Biostatistics, School of Public Health, Fudan University, Shanghai, China.
[7] Key Laboratory of Hand Reconstruction, Ministry of Health, Shanghai, China.
[8] Shanghai Key Laboratory of Peripheral Nerve and Microsurgery, Shanghai, China.
[9] State Key Laboratory of Medical Neurobiology, Fudan University, Shanghai, China.
[10] Shanghai Engineering Research Center of Artificial Intelligence Medical Auxiliary Equipment.
[11] Department of Rehabilitation, Shanghai Xuhui Central Hospital, Shanghai, China.
[12] Department of Rehabilitation, Huadong Hospital Affiliated to Fudan University, Shanghai, China.
[13] Department of Rehabilitation, Shanghai Pudong Hospital, Shanghai, China.

†These authors have contributed equally to this work and share first authorship.

***Corresponding Author:**
Prof. Wendong Xu
Email: wendongxu@fudan.edu.cn
Postal address: Department of Handsurgery, Huashan Hospital, Fudan University; No.12 Middle Wulumuqi Rd., Shanghai, China.

Keywords: chronic post-stroke aphasia, C7 neurotomy (NC7) at the intervertebral foramen, intensive speech and language therapy (iSLT), neuroplasticity

Word count: 4448

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 control trial 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≥ 12 months, aphasia quotient of Western Aphasia Battery [WAB] score ≤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 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[1]. More than 10 million new stroke cases are reported each year globally[2], and at least one-third of these patients have symptoms of aphasia[3]. Aphasia is one of the most devastating symptoms in stroke survivors[4 5], 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[3 6]. The presence of aphasia predicts the care and rehabilitation needs[7] and the likelihood of failure to return to work[8]. Aphasia increases the burden on family and society.

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

the chronic phase in half of the patients at least[15].

Although most aphasia therapy studies have enrolled chronic patients, it seems likely that earlier aphasia therapy is also effective, as it has achieved good results in improving aphasia after stroke[16]. Common aphasia rehabilitation treatments include classic speech-language rehabilitation training, as well as low-frequency electrical stimulation therapy, repetitive transcranial magnetic stimulation and transcranial direct current stimulation. Many clinical studies[17 18] have shown that speech and language therapy (SLT) effectively improves communication, reading, writing, and language expression in post-stroke aphasia patients, while the high-intensity and long-term mode may have better effects[19]. A large-scale randomised control trial (RCT) study reported that[18], 3 weeks of intensive speech and language therapy (iSLT) showed treatment effects in patients with chronic post-stroke aphasia, and significantly enhanced verbal communication among people aged 70 years or younger. This beneficial outcome could be maintained for up to 6 months after treatment. Stahl[20] further determined the optimal daily dosage and total duration of iSLT. The results showed no added value from more than 2 hours of daily SLT within 4 weeks. In addition, non-invasive brain stimulation therapy is widely used in the rehabilitation of various neurological diseases. Transcranial direct current stimulation (tDCS) uses electrode pads to deliver a weak direct current to specific brain regions of patients, which can affect the function of the cerebral cortex and help improve the accuracy of noun naming in patients with aphasia[21-23]. However, there is still a lack of enough data on the optimal sample size and a strict methodology. Low-frequency repetitive transcranial magnetic stimulation (rTMS) is the regular and repeated application of a pulsed magnetic field that briefly penetrates the skull to specific cortical regions and induces plastic changes in the brain and language function in long-term post-stroke aphasia patients. However, its efficacy is still controversial and needs further confirmation by large-scale clinical trials[24].

We previously developed a surgical procedure for contralateral C7 transfer from the nonparalyzed side to the paralyzed side (contralateral C7 to C7 cross nerve transfer [CC7]), after which patients

demonstrated improved motor function and reduced spasticity in the paralyzed arm over 12 months[25]. So far, more than 1,000 patients have undergone this surgery[26]. In addition to arm motor recovery, the improvement of language was frequently self-reported by patients and caregivers during the follow-up, and it would occur very rapidly after CC7 treatment. A few days is far from enough time for the transferred C7 nerve to regenerate[27]; therefore, we assumed that the rapid improvement of language function was mediated by the C7 neurotomy (NC7) on the paralyzed side (right side) rather than nerve regeneration. During the CC7 operation[28], to make the C7 nerve on the paralyzed side can provide more nerve fibre lenght, we cut the C7 nerve root at the intervertebral foramen. Based on anatomical research, the anterior and posterior roots converge into spinal nerves at the intervertebral foramen, and the posterior roots enlarge near the intervertebral foramen to form ganglia, also known as dorsal root ganglion (DRG)[29 30]. The exact location of neurotomy is at the transitional junction of the C7 nerve root with DRG [31]. The human C7 nerve contains 80,000 fibers[32], 94% of which are sensory fibres emitted by DRG[33]. Hence, the neurotomy of the C7 nerve root at the junction with DRG can block the ascending sensory pathway from the affected limb to the brain. The mechanisms of language production are complex. The corresponding brain regions and circuits involved in human language function are still unsolved mysteries, “How did speech evolve and what parts of the brain control it?” listed in the 125 scientific questions by “Science” journal (https://www.science.org/content/resource/125-questions-exploration-and-discovery, Page 34, Chapter Neuroscience, Q3). Based on the anatomy of brain functional areas, we hypothesized that, since the sensory-motor centre is adjacent to the language centre, if the sensory-motor centre would be changed artificially by NC7 at the intervertebral foramen, then it is possible to induce the language centre and produce related functional changes. It may also be that NC7 leads to a change in the interhemispheric balance, thus, affecting the functional neural circuits of language. We designed this trial to evaluate the surgical effect of NC7 at the intervertebral foramen on underlying neuroplasticity in patients with chronic post-stroke aphasia. Meanwhile, the iSLT is used as the

control method we will assess the effect of intensive intervention after 3 weeks and the maintenance of the effect after 6 months in both groups. Meanwhile, we use neuroimaging methods to provide objective data as evidence to support our hypothesis.

Aims of the study

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

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

METHODS AND ANALYSIS

Trial design

This study is a multicentre, randomised controlled trial with two parallel groups and a 6-month follow-up. Based on language and motor function analysis, the protocol compares patients with chronic aphasia treated with theNC7 at the intervertebral foramen and iSLT (Group A), with a control group participating in iSLT alone (Group B). The participants will be randomly allocated to one of the two groups (NC7+iSLT group or iSLT alone group) with a ratio of 1:1. The study is conducted in collaboration with the Speech Therapy Committee of the Shanghai Association of Rehabilitation Medicine, and the participants will be recruited from rehabilitation facilities of this organization. Patients will receive an indication for outpatient rehabilitation treatment at any of the

four centres (Supplemental Table 1), based on the eligibility criteria listed below. The potentially eligible patients will be invited to participate in the study via a text message after signing an informed consent.

Eligibility criteria

Inclusion criteria:

1) Aphasia for over 12 months after a single onset of infarction or haemorrhage of the left hemisphere, confirmed by magnetic resonance imaging;

2) Age: 40-65 years, sex: male or female, right-handed, native Chinese speaker;

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

4) Severity score assessed by BDAE test: level 1 and above;

5) Good compliance and ability to cooperate with language rehabilitation training;

6) Ability to fully understand and agree with the doctor's treatment plan and sign the informed consent.

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

Exclusion criteria:

1) Surgical contraindications (any reason) determined by a qualified anaesthesiologist or clinician;

2) A history of aphasia before the last onset of the stroke;

3) Serious, untreated mental illness;

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

5) Presenting contraindications for EEG and MRI evaluation;

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

7) Severe motor speech disorder and hearing impairment;

8) Having received intensive post-stroke rehabilitation therapy 4 weeks before recruitment.

Interventions

NC7 at the intervertebral foramen

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

iSLT Rehabilitation

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

Study setting

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

days later. The total perioperative period is one week. Meanwhile, patients of Group B are awaiting the therapy programme, and also receive a short-term efficacy assessment after 3 days later. The iSLT and upper extremity motor rehabilitation programme are provided for patients in both groups. After a 3-week inpatient invention, all the patients receive primary endpoint assessments, and then they continue to receive conventional low-intensity SLT at home or in other centres. For arm motor function follow-up, patients are guided to perform the rehabilitation programme consistently while a therapist or caregiver records the intensity and duration of the therapy. Six months later, all patients will receive an interim evaluation by a trained therapist from an independent team on their second visit. Afterwards, the NC7 and postoperative rehabilitation programme, which is consistent with Group A, are performed in patients of Group B. Likewise, these patients will receive a short-term and long-term follow-up for efficacy assessment. The schedule of enrolment, interventions and assessments are presented in Table 1.

Participant timeline

The schedule is presented in Table 1.

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

NC7+iSLT (Group A: experimental group)					
TIMEPOINT	**Visit 1 (Eligibility screen)**	**Visit 2 (Baseline)**	**Visit 3 (3d+1d post-NC7)**	**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			√	√	√
iSLT alone (Group B: control group)					
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

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 chose the validated Chinese version of BNT[34 35].

The secondary outcomes include aphasia quotient, daily communication (Communication Activities of Daily Living–Third Edition [CADL-3]), activities of daily living (Barthel Index), speech language function assessment (ICF[36] speech language function assessment), post-stroke depression assessment (Hamilton Rating Scale for Depression, HRSD) and safety outcomes in different groups. Assessments performed to collect data for the primary, secondary, and safety outcomes are listed in Table 2.

Table 2. Assessments performed to collect data for the primary, secondary, and safety outcomes

Variable	Measure
Primary outcome	
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.
Secondary outcome	
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
Post-stroke Depression assessment	Change from baseline in Hamilton Rating Scale for Depression (HRSD-24) score
Safety outcomes	
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.

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.

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[17 20], the naming score can be improved after intensive speech therapy and verified after non-invasive brain stimulation therapy[22 23]. Combined with our previous data, it is assumed that postoperative (NC7) followed by rehabilitation (iSLT) can improve the naming ability with an average score of 2.04 ± 1.03 points. In comparison, the iSLT-alone group can improve the naming ability with an average score of 0.7 ± 0.24 points. With the power of 90% and the 5% significant level (two-sided), the sample size of each group was 21. With a loss to follow-up rate of 15%, the total maximum sample size was 50 cases.

Statistical analysis

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

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

ETHICS AND DISSEMINATION

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

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

Patient and public involvement

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

DISCUSSION

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

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

found that the naming ability of patients after CC7 was significantly improved, and many other researchers also used the correct spontaneous naming scores as the only BNT-related index for evaluating language function[39 40]. In this study, we use the BNT scale as an evaluation index for language function for the primary outcome, and we will use WAB, CADL Communication Scale, ADL Scale, and Post-Stroke Depression Scale scores as secondary indicators in the aspects of language repetition, listening comprehension, communication ability, daily life, and psychology. The ICF speech and language function assessment can detect the degree of changes in voice intonation, oral motor ability, articulation intelligibility, and oral expression of patients to exclude the possible reduction of spasticity after neurotomy for the interference with study results.

The CC7 was first invented by Gu[41-43] to treat limb dysfunction after brachial plexus injury, and the follow-up work[44 45] showed neuroplastic changes between the hemispheres after surgery. Based on this theoretical perspective, Xu originally proposed the scientific viewpoint that "One hemisphere controls both limbs" and expanded the development of the "contralateral C7 nerve transfer" to "contralateral C7 to C7 cross nerve transfer" for treating central hemiplegia[25 46 47]. Our previous investigations suggested the possible correlation between CC7 and the improvement of chronic aphasia, an effect occurring in the early postoperative period; thus, the possibility of aphasia recovery after NC7 at the intervertebral foramen caught our attention. In this study, we measured muscle strength, joint range of motion, upper limb MAS score and sensory assessment as safety indicators to evaluate the effect of the NC7 on the right side. If the NC7 does improve language function with no physical dysfunction, it will provide an entirely novel perspective for the treatment of chronic post-stroke aphasia. However, the mechanisms involved in NC7 effectiveness in chronic aphasia are not fully understood. We consider that this clinical phenomenon of language function improvement is related to NC7 stimulating neuroplasticity. This requires more objective functional imaging evidence to confirm. Several recent publications review the mechanisms of aphasia recovery. In some cases, the therapy mechanisms [48 49] are evidenced by changes in task-related

brain activations or changes in functional connectivity within functional networks[50 51]. Here, we use fMRI and EEG methods in relation to the naming ability and semantic prediction to investigate the neural and physiological states induced by changes in the language function after NC7.

In conclusion, this is the first RCT to evaluate the surgical effect in patients with chronic post-stroke aphasia for whom there is no effective treatment available. If found to be efficient, this strategy could be regularly implemented due to its easy application and low cost. Moreover, larger trials could be extended to other diseases with a central nerve injury to assess for this strategy's efficiency on language and other functions. Once our hypothesis is confirmed, this trial will provide important evidence for supporting NC7 at the intervertebral foramen as a novel treatment approach for chronic aphasia. A limitation of this study is that it is not double-blind but evaluator-blind, and the experimental group may involve a minor placebo effect. To offset the short-term placebo effect after surgery, we conducted a secondary endpoint assessment at 6 months. At that time, the patient's placebo effect due to invasive interventions will be greatly reduced.

Abbreviations list

RCT = randomised controlled trials; CC7 = contralateral C7 to C7 cross nerve transfer; NC7 = C7 neurotomy; iSLT = intensive speech and language therapy; DRG=dorsal root ganglion; BDAE= Boston Diagnostic Aphasia Examination; BNT = Boston naming test; WAB = Western Aphasia Battery; CADL = Communication Activities of Daily Living; ADL= Activity of Daily Living; ICF=International classification of Functioning, Disability and Health; HRSD= Hamilton Rating Scale for Depression, EEG = Electroencephalography; fMRI = functional magnetic resonance imaging; SAE = Severe Adverse Events.

Competing Interests

None declared.

Patient consent for publication

Not required.

Funding

This work was supported by Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2019-I2M-5-007), Chinese Academy of Medical Sciences Special Project of Clinical and Translational Medicine research cultivating program(2021-I2M-C&T-B-100), National Natural Science Foundation of China (81830063, 82021002) and Shanghai Clinical Research Center for Aging and Medicine (19MC1910500).

Acknowledgements

We would like to thank all the study participants, our colleagues at Huashan Hospital, Fudan University and all the participating institutions.

Contributors

WX is the principal investigator of this study and refined the protocol. TL and JF wrote the manuscript and contributed to the design of the study. ML, the medical statistician for the study, contributed to the statistical design and ethical approval. WC contributed to brain plasticity evaluation design and guidance. YG participated in the concept and design of the study. RH, XM, WQ, YZ, XC, LD have revised the protocol critically for multicentre intellectual content. All authors read and approved the final manuscript.

REFERENCES

1. Stefaniak JD, Halai AD, Lambon Ralph MA. The neural and neurocomputational bases of recovery from post-stroke aphasia. *Nat Rev Neurol* 2020;**16**(1):43-55.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017;**135**(10):e146-e603.

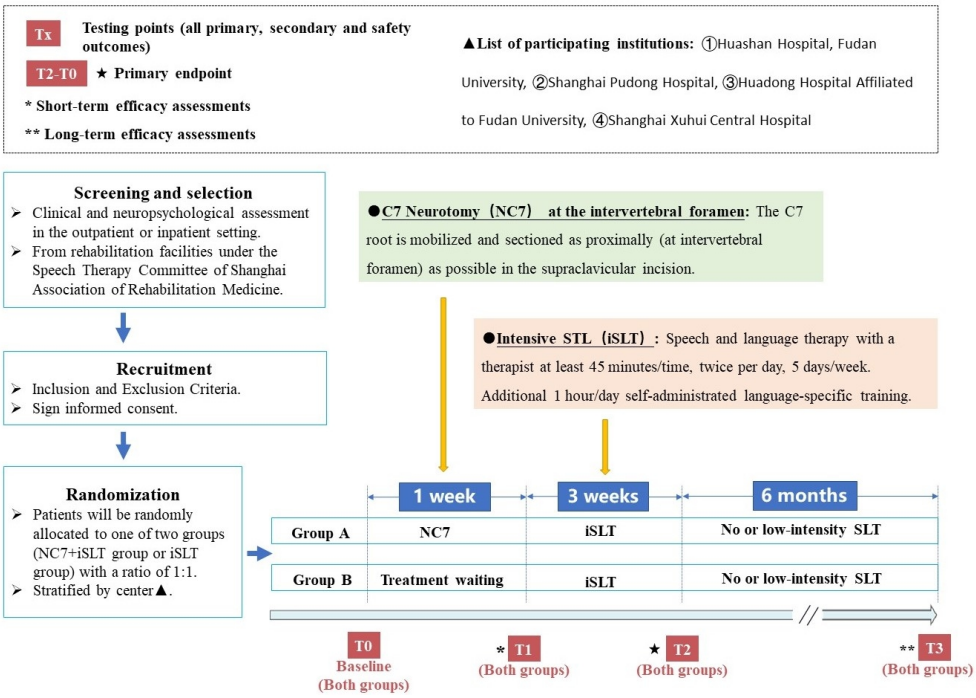
3. Engelter ST, Gostynski M, Papa S, et al. Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis. *Stroke; a journal of cerebral circulation* 2006;**37**(6):1379-84.
4. Hilari K. The impact of stroke: are people with aphasia different to those without? *Disability and rehabilitation* 2011;**33**(3):211-8.
5. Pollock A, St George B, Fenton M, et al. Top ten research priorities relating to life after stroke. *The Lancet Neurology* 2012;**11**(3):209.
6. Flowers HL, Skoretz SA, Silver FL, et al. Poststroke Aphasia Frequency, Recovery, and Outcomes: A Systematic Review and Meta-Analysis. *Archives of physical medicine and rehabilitation* 2016;**97**(12):2188-201.e8.
7. Bonilha HS, Simpson AN, Ellis C, et al. The one-year attributable cost of post-stroke dysphagia. *Dysphagia* 2014;**29**(5):545-52.
8. Doucet T, Muller F, Verdun-Esquer C, et al. Returning to work after a stroke: a retrospective study at the Physical and Rehabilitation Medicine Center La Tour de Gassies. *Annals of physical and rehabilitation medicine* 2012;**55**(2):112-27.
9. Murray LL. Attention and other cognitive deficits in aphasia: presence and relation to language and communication measures. *American journal of speech-language pathology* 2012;**21**(2):S51-64.
10. Yagata SA, Yen M, McCarron A, et al. Rapid recovery from aphasia after infarction of Wernicke's area. *Aphasiology* 2017;**31**(8):951-80.
11. Elkana O, Frost R, Kramer U, et al. Cerebral language reorganization in the chronic stage of recovery: a longitudinal fMRI study. *Cortex; a journal devoted to the study of the nervous system and behavior* 2013;**49**(1):71-81.
12. Pedersen PM, Jørgensen HS, Nakayama H, et al. Aphasia in acute stroke: incidence, determinants, and recovery. *Ann Neurol* 1995;**38**(4):659-66.
13. Laska AC, Hellblom A, Murray V, et al. Aphasia in acute stroke and relation to outcome. *Journal of internal medicine* 2001;**249**(5):413-22.
14. El Hachioui H, Visch-Brink EG, de Lau LM, et al. Screening tests for aphasia in patients with stroke: a systematic review. *Journal of neurology* 2017;**264**(2):211-20.
15. Wade DT, Hewer RL, David RM, et al. Aphasia after stroke: natural history and associated deficits. *J Neurol Neurosurg Psychiatry* 1986;**49**(1):11-6.
16. Fridriksson J, Hillis AE. Current Approaches to the Treatment of Post-Stroke Aphasia. *J Stroke* 2021;**23**(2):183-201.
17. Brady MC, Kelly H, Godwin J, et al. Speech and language therapy for aphasia following stroke. *The Cochrane database of systematic reviews* 2016;**2016**(6):Cd000425.
18. Breitenstein C, Grewe T, Flöel A, et al. Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *Lancet (London, England)* 2017;**389**(10078):1528-38.
19. Doppelbauer L, Mohr B, Dreyer FR, et al. Long-Term Stability of Short-Term Intensive Language-Action Therapy in Chronic Aphasia: A 1-2 year Follow-Up Study. *Neurorehabilitation and neural repair* 2021;**35**(10):861-70.
20. Stahl B, Mohr B, Büscher V, et al. Efficacy of intensive aphasia therapy in patients with chronic stroke: a randomised controlled trial. *J Neurol Neurosurg Psychiatry* 2018;**89**(6):586-92.
21. Elsner B, Kugler J, Pohl M, et al. Transcranial direct current stimulation (tDCS) for improving aphasia in adults with aphasia after stroke. *The Cochrane database of systematic reviews* 2019;**5**(5):Cd009760.
22. Fridriksson J, Rorden C, Elm J, et al. Transcranial Direct Current Stimulation vs Sham Stimulation to Treat Aphasia After Stroke: A Randomised Clinical Trial. *JAMA neurology* 2018;**75**(12):1470-76.

23. Meinzer M, Darkow R, Lindenberg R, et al. Electrical stimulation of the motor cortex enhances treatment outcome in post-stroke aphasia. *Brain : a journal of neurology* 2016;**139**(Pt 4):1152-63.
24. Heikkinen PH, Pulvermüller F, Mäkelä JP, et al. Combining rTMS With Intensive Language-Action Therapy in Chronic Aphasia: A Randomised Controlled Trial. *Frontiers in neuroscience* 2018;**12**:1036.
25. Zheng MX, Hua XY, Feng JT, et al. Trial of Contralateral Seventh Cervical Nerve Transfer for Spastic Arm Paralysis. *The New England journal of medicine* 2018;**378**(1):22-34.
26. Feng J, Li T, Lv M, et al. Reconstruction of paralyzed arm function in patients with hemiplegia through contralateral seventh cervical nerve cross transfer: a multicenter study and real-world practice guidance. *EClinicalMedicine* 2022;**43**:101258.
27. Maas MB, Lev MH, Ay H, et al. The prognosis for aphasia in stroke. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 2012;**21**(5):350-7.
28. Wen-Dong X. Surgical Technique of Xu's CC7 Procedure "Contralateral C7 to C7 Cross Nerve Transfer Through a Trans Longus Colli, Prespinal Route for Treating Spastic Arm". *Operative Neurosurgery* 2020(1):1.
29. Leijnse JN, D'Herde K. Revisiting the segmental organization of the human spinal cord. *Journal of anatomy* 2016;**229**(3):384-93.
30. Takahashi K, Ninomiya T. Morphological changes of dorsal root ganglion cells in the process-forming period. *Prog Neurobiol* 1987;**29**(4):393-410.
31. Zhong LY, Wang AP, Hong L, et al. Microanatomy of the brachial plexus roots and its clinical significance. *Surgical and radiologic anatomy : SRA* 2017;**39**(6):601-10.
32. Gesslbauer B, Hruby LA, Roche AD, et al. Axonal components of nerves innervating the human arm. *Ann Neurol* 2017;**82**(3):396-408.
33. Mille-Hamard L, Bauchet L, Baillet-Derbin C, et al. Estimation of the number and size of female adult rat C4, C5 and C6 dorsal root ganglia (DRG) neurons. *Somatosensory & motor research* 1999;**16**(3):223-8.
34. Cheung RW, Cheung MC, Chan AS. Confrontation naming in Chinese patients with left, right or bilateral brain damage. *Journal of the International Neuropsychological Society : JINS* 2004;**10**(1):46-53.
35. Chen TB, Lin CY, Lin KN, et al. Culture qualitatively but not quantitatively influences performance in the Boston naming test in a chinese-speaking population. *Dementia and geriatric cognitive disorders extra* 2014;**4**(1):86-94.
36. Pike C, Kritzinger A, Pillay B. Social participation in working-age adults with aphasia: an updated systematic review. *Topics in stroke rehabilitation* 2017;**24**(8):627-39.
37. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet (London, England)* 2019;**394**(10204):1145-58.
38. Fridriksson J, den Ouden DB, Hillis AE, et al. Anatomy of aphasia revisited. *Brain : a journal of neurology* 2018;**141**(3):848-62.
39. Rossi A, Burkhart C, Dell-Kuster S, et al. Serum anticholinergic activity and postoperative cognitive dysfunction in elderly patients. *Anesthesia and analgesia* 2014;**119**(4):947-55.
40. Nousia A, Siokas V, Aretouli E, et al. Beneficial Effect of Multidomain Cognitive Training on the Neuropsychological Performance of Patients with Early-Stage Alzheimer's Disease. *Neural plasticity* 2018;**2018**:2845176.
41. Gu YD, Zhang GM, Chen DS, et al. Seventh cervical nerve root transfer from the contralateral healthy side for treatment of brachial plexus root avulsion. *Journal of hand surgery (Edinburgh, Scotland)* 1992;**17**(5):518-21.

42. Gu Y, Xu J, Chen L, et al. Long term outcome of contralateral C7 transfer: a report of 32 cases. *Chinese medical journal* 2002;**115**(6):866-8.
43. Gu YD. Contralateral C7 root transfer over the last 20 years in China. *Chinese medical journal* 2007;**120**(13):1123-6.
44. Hua XY, Liu B, Qiu YQ, et al. Long-term ongoing cortical remodeling after contralateral C-7 nerve transfer. *Journal of neurosurgery* 2013;**118**(4):725-9.
45. Jiang S, Li ZY, Hua XY, et al. Reorganization in motor cortex after brachial plexus avulsion injury and repair with the contralateral C7 root transfer in rats. *Microsurgery* 2010;**30**(4):314-20.
46. Xu WD, Hua XY, Zheng MX, et al. Contralateral C7 nerve root transfer in treatment of cerebral palsy in a child: case report. *Microsurgery* 2011;**31**(5):404-8.
47. Hua XY, Qiu YQ, Li T, et al. Contralateral peripheral neurotization for hemiplegic upper extremity after central neurologic injury. *Neurosurgery* 2015;**76**(2):187-95; discussion 95.
48. Nardo D, Holland R, Leff AP, et al. Less is more: neural mechanisms underlying anomia treatment in chronic aphasic patients. *Brain : a journal of neurology* 2017;**140**(11):3039-54.
49. Crinion JT, Leff AP. Using functional imaging to understand therapeutic effects in poststroke aphasia. *Current opinion in neurology* 2015;**28**(4):330-7.
50. Kiran S, Meier EL, Johnson JP. Neuroplasticity in Aphasia: A Proposed Framework of Language Recovery. *Journal of speech, language, and hearing research : JSLHR* 2019;**62**(11):3973-85.
51. Hartwigsen G, Saur D. Neuroimaging of stroke recovery from aphasia - Insights into plasticity of the human language network. *Neuroimage* 2019;**190**:14-31.

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

Major research institution	**Name of institutional review board**
Huashan Hospital, Fudan University	Institutional Review Board of Huashan Hospital Affiliated to Fudan University
Sub-centre research institution	**Name of institutional review board**
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

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	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

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
	6b	Explanation for choice of comparators	3-6
Objectives	7	Specific objectives or hypotheses	6, 7
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8,9
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13-14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8,9
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
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

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8,9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
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	10,11
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	10,11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10,11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
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
	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

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14,15
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____NA_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
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_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____18____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____13,14_____
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_____
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_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____NA_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Supplemental Material__
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_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065173.R2
Article Type:	Protocol
Date Submitted by the Author:	03-Mar-2023
Complete List of Authors:	Li, Tie; Huashan Hospital Fudan University Department of Hand Surgery Feng, Juntao; Huashan Hospital Fudan University Department of Hand Surgery Hu, Ruiping; Huashan Hospital Fudan University, Department of Rehabilitation Lv, Minzhi; Fudan University, Center of Evidence-Based Medicine, Department of Biostatistics, School of Public Health Chang, Wenshuo; Shanghai International Studies University, Institute of Linguistics Ma, Xingyi; Huashan Hospital Fudan University, Handsurgery Qi, Wenjun; Huashan Hospital Fudan University Zhang, Ying; Shanghai Xuhui Central Hospital, Department of Rehabilitation Chen, Xiuen; Huadong Hospital Affiliated to Fudan University, Department of Rehabilitation Ding, Ling; Shanghai Pudong Hospital, Department of Rehabilitation Gu, Yudong; Huashan Hospital Fudan University Department of Hand Surgery Xu, Wendong; Huashan Hospital Fudan University, Handsurgery
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Surgery
Keywords:	Stroke < NEUROLOGY, Neurosurgery < SURGERY, Clinical trials < THERAPEUTICS

TITLE PAGE

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

Authors:

Tie Li[1-3,7-10†], Juntao Feng[1-3,7-10†], Ruiping Hu[4], Minzhi Lv[6], Wenshuo Chang[5], Xingyi Ma[1,2], Wenjun Qi[1,2], Ying Zhang[11], Xiuen Chen[12], Ling Ding[13], Yudong Gu[1-3,7-10], Wendong Xu[1-3,7-10*]

[1] Department of Hand Surgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China.
[2] Department of Hand and Upper Extremity Surgery, Limb Function Reconstruction Center, Jing'an District Central Hospital, Shanghai, China.
[3] National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University.
[4] Department of Rehabilitation, Huashan Hospital, Shanghai Medical College, Fudan University Shanghai, China.
[5] Institute of Linguistics, Shanghai International Studies University, Shanghai, China.
[6] Center of Evidence-Based Medicine, Department of Biostatistics, School of Public Health, Fudan University, Shanghai, China.
[7] Key Laboratory of Hand Reconstruction, Ministry of Health, Shanghai, China.
[8] Shanghai Key Laboratory of Peripheral Nerve and Microsurgery, Shanghai, China.
[9] State Key Laboratory of Medical Neurobiology, Fudan University, Shanghai, China.
[10] Shanghai Engineering Research Center of Artificial Intelligence Medical Auxiliary Equipment.
[11] Department of Rehabilitation, Shanghai Xuhui Central Hospital, Shanghai, China.
[12] Department of Rehabilitation, Huadong Hospital Affiliated to Fudan University, Shanghai, China.
[13] Department of Rehabilitation, Shanghai Pudong Hospital, Shanghai, China.

†These authors have contributed equally to this work and share first authorship.

***Corresponding Author:**
Prof. Wendong Xu
Email: wendongxu@fudan.edu.cn
Postal address: Department of Handsurgery, Huashan Hospital, Fudan University; No.12 Middle Wulumuqi Rd., Shanghai, China.

Keywords: chronic post-stroke aphasia, C7 neurotomy (NC7) at the intervertebral foramen, intensive speech and language therapy (iSLT), neuroplasticity

Word count: 4396

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≥ 12 months, aphasia quotient of Western Aphasia Battery [WAB] score ≤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[1]. More than 10 million new stroke cases are reported each year globally[2], and at least one-third of these patients have symptoms of aphasia[3]. Aphasia is one of the most devastating symptoms in stroke survivors[4 5], 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[3 6]. The presence of aphasia predicts the care and rehabilitation needs[7] and the likelihood of failure to return to work[8]. Aphasia increases the burden on family and society.

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

the chronic phase in half of the patients at least[15].

Although most aphasia therapy studies have enrolled chronic patients, it seems likely that earlier aphasia therapy is also effective, as it has achieved good results in improving aphasia after stroke[16]. Common aphasia rehabilitation treatments include classic speech-language rehabilitation training, as well as low-frequency electrical stimulation therapy, repetitive transcranial magnetic stimulation and transcranial direct current stimulation. Many clinical studies[17 18] have shown that speech and language therapy (SLT) effectively improves communication, reading, writing, and language expression in post-stroke aphasia patients, while the high-intensity and long-term mode may have better effects[19]. A large-scale randomised control trial (RCT) study reported that[18], 3 weeks of intensive speech and language therapy (iSLT) showed treatment effects in patients with chronic post-stroke aphasia, and significantly enhanced verbal communication among people aged 70 years or younger. This beneficial outcome could be maintained for up to 6 months after treatment. Stahl[20] further determined the optimal daily dosage and total duration of iSLT. The results showed no added value from more than 2 hours of daily SLT within 4 weeks. In addition, non-invasive brain stimulation therapy is widely used in the rehabilitation of various neurological diseases. Transcranial direct current stimulation (tDCS) uses electrode pads to deliver a weak direct current to specific brain regions of patients, which can affect the function of the cerebral cortex and help improve the accuracy of noun naming in patients with aphasia[21-23]. However, there is still a lack of enough data on the optimal sample size and a strict methodology. Low-frequency repetitive transcranial magnetic stimulation (rTMS) is the regular and repeated application of a pulsed magnetic field that briefly penetrates the skull to specific cortical regions and induces plastic changes in the brain and language function in long-term post-stroke aphasia patients. However, its efficacy is still controversial and needs further confirmation by large-scale clinical trials[24].

We previously developed a surgical procedure for contralateral C7 transfer from the nonparalyzed side to the paralyzed side (contralateral C7 to C7 cross nerve transfer [CC7]), after which patients

demonstrated improved motor function and reduced spasticity in the paralyzed arm over 12 months[25]. So far, more than 1,000 patients have undergone this surgery[26]. In addition to arm motor recovery, the improvement of language was frequently self-reported by patients and caregivers during the follow-up, and it would occur very rapidly after CC7 treatment. A few days is far from enough time for the transferred C7 nerve to regenerate[27]; therefore, we assumed that the rapid improvement of language function was mediated by the C7 neurotomy (NC7) on the paralyzed side (right side) rather than nerve regeneration. During the CC7 operation[28], to make the C7 nerve on the paralyzed side can provide more nerve fibre length, we cut the C7 nerve root at the intervertebral foramen. Based on anatomical research, the anterior and posterior roots converge into spinal nerves at the intervertebral foramen, and the posterior roots enlarge near the intervertebral foramen to form ganglia, also known as dorsal root ganglion (DRG)[29 30]. The exact location of neurotomy is at the transitional junction of the C7 nerve root with DRG [31]. The human C7 nerve contains 80,000 fibers[32], 94% of which are sensory fibres emitted by DRG[33]. Hence, the neurotomy of the C7 nerve root at the junction with DRG can block the ascending sensory pathway from the affected limb to the brain. Based on the anatomy of brain functional areas, we hypothesized that, since the sensory-motor centre is adjacent to the language centre, if the sensory-motor centre would be changed artificially by NC7 at the intervertebral foramen, then it is possible to induce the language centre and produce related functional changes. It may also be that NC7 leads to a change in the interhemispheric balance, thus, affecting the functional neural circuits of language. We designed this trial to evaluate the surgical effect of NC7 at the intervertebral foramen on underlying neuroplasticity in patients with chronic post-stroke aphasia. Meanwhile, the iSLT is used as the control method we will assess the effect of intensive intervention after 3 weeks and the maintenance of the effect after 6 months in both groups. Meanwhile, we use neuroimaging methods to provide objective data as evidence to support our hypothesis.

Aims of the study

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

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

METHODS AND ANALYSIS

Trial design

This study is a multicentre, randomised controlled trial with two parallel groups and a 6-month follow-up. Based on language and motor function analysis, the protocol compares patients with chronic aphasia treated with the NC7 at the intervertebral foramen and iSLT (Group A), with a control group participating in iSLT alone (Group B). The participants will be randomly allocated to one of the two groups (NC7+iSLT group or iSLT alone group) with a ratio of 1:1. The study is conducted in collaboration with the Speech Therapy Committee of the Shanghai Association of Rehabilitation Medicine, and the participants will be recruited from rehabilitation facilities of this organization. Patients will receive an indication for outpatient rehabilitation treatment at any of the four centres (Supplemental Table 1), based on the eligibility criteria listed below. The potentially eligible patients will be invited to participate in the study via a text message after signing an informed consent.

Eligibility criteria

Inclusion criteria:

1) Aphasia for over 12 months after a single onset of infarction or haemorrhage of the left hemisphere, confirmed by magnetic resonance imaging;

2) Age: 40-65 years, sex: male or female, right-handed, native Chinese speaker;

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

4) Severity score assessed by BDAE test: level 1 and above;

5) Good compliance and ability to cooperate with language rehabilitation training;

6) Ability to fully understand and agree with the doctor's treatment plan and sign the informed consent.

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

Exclusion criteria:

1) Surgical contraindications (any reason) determined by a qualified anaesthesiologist or clinician;

2) A history of aphasia before the last onset of the stroke;

3) Serious, untreated mental illness;

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

5) Presenting contraindications for EEG and MRI evaluation;

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

7) Severe motor speech disorder and hearing impairment;

8) Having received intensive post-stroke rehabilitation therapy 4 weeks before recruitment.

Interventions

NC7 at the intervertebral foramen

Make a 6-cm long longitudinal incision along the medial border of the sternocleidomastoid muscle on the right side after the cervical plexus under anaesthesia/general anaesthesia (depending on the patient's preference and the anaesthesiologist's risk assessment). Carefully separate the structure layer by layer and identify the brachial plexus by marking the C7 nerve with a vessel loop. Next,

the C7 root is mobilized and sectioned as proximally (at the intervertebral foramen) as possible. Considering that some patients have limb hemiplegia, CC7 surgery may be required to improve limb function at the end of this trial. Therefore, we fix the severed C7 root to the fascia at the junction of the scapulohyoid and sternocleidomastoid muscles with silk thread, making it easier to find and anastomose with the contralateral C7 root during the later CC7[28] surgical intervention.

iSLT Rehabilitation

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

Study setting

This study started on July 2022, participants will be recruited between July 2022 and July 2023. Study completion is expected to be July 2024. A total of 50 patients diagnosed with chronic aphasia and hemiplegia after stroke will be recruited. Patients in the research institutions will receive in-hospital treatment for 3 to 4 weeks, with follow-up assessment at 6 months (Figure 1). Patients will be selected based on the study eligibility criteria on their first visit. Then, eligible patients will be randomly assigned to one of the two groups in different centres. Patients of Group A will receive NC7 immediately after assignment and receive a short-term efficacy assessment 3 days later. The total perioperative period is one week. Meanwhile, patients of Group B are awaiting the therapy programme, and also receive a short-term efficacy assessment after 3 days later. The iSLT and upper extremity motor rehabilitation programme are provided for patients in both groups. After a 3-week inpatient invention, all the patients receive primary endpoint assessments, and then they continue to receive conventional low-intensity SLT at home or in other centres. For arm motor

function follow-up, patients are guided to perform the rehabilitation programme consistently while a therapist or caregiver records the intensity and duration of the therapy. Six months later, all patients will receive an interim evaluation by a trained therapist from an independent team on their second visit. Afterwards, the NC7 and postoperative rehabilitation programme, which is consistent with Group A, are performed in patients of Group B. Likewise, these patients will receive a short-term and long-term follow-up for efficacy assessment. The schedule of enrolment, interventions and assessments are presented in Table 1.

Participant timeline

The schedule is presented in Table 1.

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

NC7+iSLT (Group A: experimental group)					
TIMEPOINT	**Visit 1 (Eligibility screen)**	**Visit 2 (Baseline)**	**Visit 3 (3d+1d post-NC7)**	**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			√	√	√
iSLT alone (Group B: control group)					

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

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 chose the validated Chinese version of BNT[34 35].

The secondary outcomes include aphasia quotient, daily communication (Communication Activities of Daily Living–Third Edition [CADL-3]), activities of daily living (Barthel Index), speech language function assessment (ICF[36] speech language function assessment), post-stroke depression assessment (Hamilton Rating Scale for Depression, HRSD) and safety outcomes in different groups. Assessments performed to collect data for the primary, secondary, and safety outcomes are listed in Table 2.

Table 2. Assessments performed to collect data for the primary, secondary, and safety outcomes

Variable	Measure
Primary outcome	
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.
Secondary outcome	
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.
Post-stroke Depression assessment	Change from baseline in Hamilton Rating Scale for Depression (HRSD-24) score.
Safety outcomes	
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.

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.

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[17 20], the naming score can be improved after intensive speech therapy and verified after non-invasive brain stimulation therapy[22 23]. 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

points in average from the literature review[37]. According to results from our phase-I study, the standard deviation was 6.0. A 2-sided 0.05 level of significance and a sample size of 40 patients (20 per group) provided 80% statistical power to demonstrate this difference in the change of BNT score from baseline. Considering a drop-out rate of 15%, we will recruit a total of 50 patients (25 per group).

Statistical analysis

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

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

ETHICS AND DISSEMINATION

Ethical approval for this trial was granted by the Institutional Review Board of Huashan Hospital, Fudan University (No. KY2021-592), and by the institutional review boards of all participating institutions (Supplemental Table 1). All patients will sign an informed consent prior to entry into the study. Patients may withdraw from the study at any time. Important protocol modifications will

be communicated to the relevant members of the research team. The procedure will be performed following the principles described in the declaration of Helsinki.

Patient and public involvement

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

DISCUSSION

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

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

ADL Scale, and Post-Stroke Depression Scale scores as secondary indicators in the aspects of language repetition, listening comprehension, communication ability, daily life, and psychology. The ICF speech and language function assessment can detect the degree of changes in voice intonation, oral motor ability, articulation intelligibility, and oral expression of patients to exclude the possible reduction of spasticity after neurotomy for the interference with study results.

The CC7 was first invented by Gu et al.[42-44] to treat limb dysfunction after brachial plexus injury, and the follow-up work[45 46] showed neuroplastic changes between the hemispheres after surgery. Based on this theoretical perspective, Xu originally proposed the scientific viewpoint that "One hemisphere controls both limbs" and expanded the development of the "contralateral C7 nerve transfer" to "contralateral C7 to C7 cross nerve transfer" for treating central hemiplegia[25 47 48]. Our previous investigations suggested the possible correlation between CC7 and the improvement of chronic aphasia, an effect occurring in the early postoperative period; thus, the possibility of aphasia recovery after NC7 at the intervertebral foramen caught our attention. In this study, we measured muscle strength, joint range of motion, upper limb MAS score and sensory assessment as safety indicators to evaluate the effect of the NC7 on the right side. If the NC7 does improve language function with no physical dysfunction, it will provide an entirely novel perspective for the treatment of chronic post-stroke aphasia. However, the mechanisms involved in NC7 effectiveness in chronic aphasia are not fully understood. We consider that this clinical phenomenon of language function improvement is related to NC7 stimulating neuroplasticity. This requires more objective functional imaging evidence to confirm. Several recent publications review the mechanisms of aphasia recovery. In some cases, the therapy mechanisms [49 50] are evidenced by changes in task-related brain activations or changes in functional connectivity within functional networks[51 52]. Here, we use fMRI and EEG methods in relation to the naming ability and semantic prediction to investigate the neural and physiological states induced by changes in the language function after NC7.

In conclusion, this is the first RCT to evaluate the surgical effect in patients with chronic post-stroke aphasia for whom there is no effective treatment available. If found to be efficient, this strategy could be regularly implemented due to its easy application and low cost. Moreover, larger trials could be extended to other diseases with a central nerve injury to assess for this strategy's efficiency on language and other functions. Once our hypothesis is confirmed, this trial will provide important evidence for supporting NC7 at the intervertebral foramen as a novel treatment approach for chronic aphasia. A limitation of this study is that it is not double-blind but evaluator-blind, and the experimental group may involve a minor placebo effect. To offset the short-term placebo effect after surgery, we conducted a secondary endpoint assessment at 6 months. At that time, the patient's placebo effect due to invasive interventions will be greatly reduced.

Abbreviations list

RCT = randomised controlled trials; CC7 = contralateral C7 to C7 cross nerve transfer; NC7 = C7 neurotomy; iSLT = intensive speech and language therapy; DRG=dorsal root ganglion; BDAE= Boston Diagnostic Aphasia Examination; BNT = Boston naming test; WAB = Western Aphasia Battery; CADL = Communication Activities of Daily Living; ADL= Activity of Daily Living; ICF=International classification of Functioning, Disability and Health; HRSD= Hamilton Rating Scale for Depression, EEG = Electroencephalography; fMRI = functional magnetic resonance imaging; SAE = Severe Adverse Events.

Competing Interests

None declared.

Patient consent for publication

Not required.

Funding

This work was supported by Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2019-I2M-5-007), Chinese Academy of Medical Sciences Special Project of Clinical and Translational Medicine research cultivating program(2021-I2M-C&T-B-100), National Natural Science Foundation of China (81830063, 82021002) and Shanghai Clinical Research Center for Aging and Medicine (19MC1910500).

Acknowledgements

We would like to thank all the study participants, our colleagues at Huashan Hospital, Fudan University and all the participating institutions.

Contributors

WX is the principal investigator of this study and refined the protocol. TL and JF wrote the manuscript and contributed to the design of the study. ML, the medical statistician for the study, contributed to the statistical design and ethical approval. WC contributed to brain plasticity evaluation design and guidance. YG participated in the concept and design of the study. RH, XM, WQ, YZ, XC, LD have revised the protocol critically for multicentre intellectual content. All authors read and approved the final manuscript.

REFERENCES

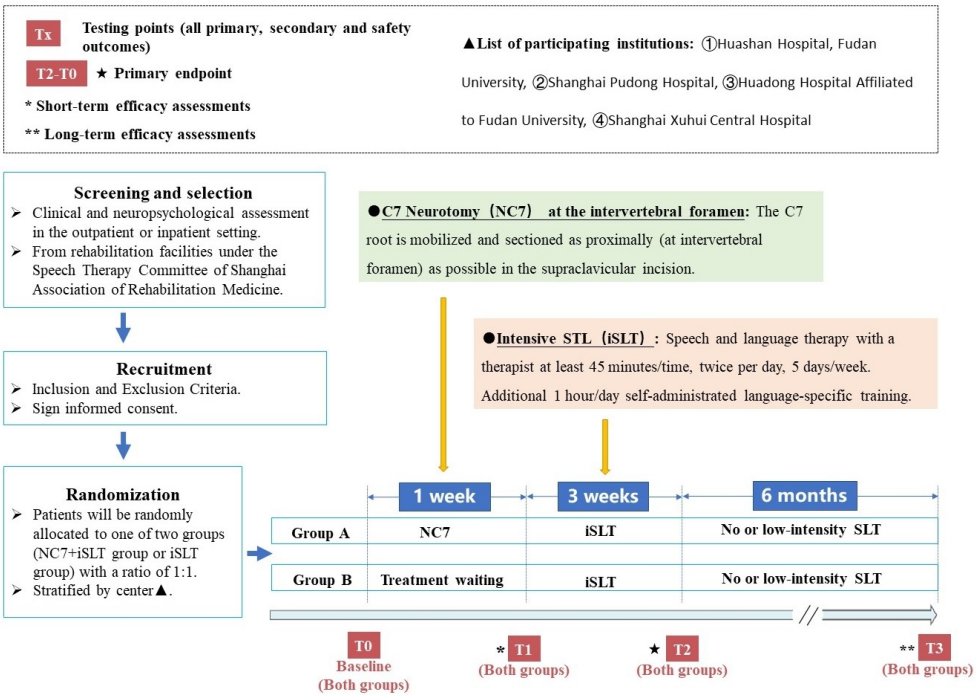
1. Stefaniak JD, Halai AD, Lambon Ralph MA. The neural and neurocomputational bases of recovery from post-stroke aphasia. *Nat Rev Neurol* 2020;**16**(1):43-55.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017;**135**(10):e146-e603.
3. Engelter ST, Gostynski M, Papa S, et al. Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis. *Stroke; a journal of cerebral circulation* 2006;**37**(6):1379-84.
4. Hilari K. The impact of stroke: are people with aphasia different to those without? *Disability and rehabilitation* 2011;**33**(3):211-8.
5. Pollock A, St George B, Fenton M, et al. Top ten research priorities relating to life after stroke. *The Lancet Neurology* 2012;**11**(3):209.

6. Flowers HL, Skoretz SA, Silver FL, et al. Poststroke Aphasia Frequency, Recovery, and Outcomes: A Systematic Review and Meta-Analysis. *Archives of physical medicine and rehabilitation* 2016;**97**(12):2188-201.e8.
7. Bonilha HS, Simpson AN, Ellis C, et al. The one-year attributable cost of post-stroke dysphagia. *Dysphagia* 2014;**29**(5):545-52.
8. Doucet T, Muller F, Verdun-Esquer C, et al. Returning to work after a stroke: a retrospective study at the Physical and Rehabilitation Medicine Center La Tour de Gassies. *Annals of physical and rehabilitation medicine* 2012;**55**(2):112-27.
9. Murray LL. Attention and other cognitive deficits in aphasia: presence and relation to language and communication measures. *American journal of speech-language pathology* 2012;**21**(2):S51-64.
10. Yagata SA, Yen M, McCarron A, et al. Rapid recovery from aphasia after infarction of Wernicke's area. *Aphasiology* 2017;**31**(8):951-80.
11. Elkana O, Frost R, Kramer U, et al. Cerebral language reorganization in the chronic stage of recovery: a longitudinal fMRI study. *Cortex; a journal devoted to the study of the nervous system and behavior* 2013;**49**(1):71-81.
12. Pedersen PM, Jørgensen HS, Nakayama H, et al. Aphasia in acute stroke: incidence, determinants, and recovery. *Ann Neurol* 1995;**38**(4):659-66.
13. Laska AC, Hellblom A, Murray V, et al. Aphasia in acute stroke and relation to outcome. *Journal of internal medicine* 2001;**249**(5):413-22.
14. El Hachioui H, Visch-Brink EG, de Lau LM, et al. Screening tests for aphasia in patients with stroke: a systematic review. *Journal of neurology* 2017;**264**(2):211-20.
15. Wade DT, Hewer RL, David RM, et al. Aphasia after stroke: natural history and associated deficits. *J Neurol Neurosurg Psychiatry* 1986;**49**(1):11-6.
16. Fridriksson J, Hillis AE. Current Approaches to the Treatment of Post-Stroke Aphasia. *J Stroke* 2021;**23**(2):183-201.
17. Brady MC, Kelly H, Godwin J, et al. Speech and language therapy for aphasia following stroke. *The Cochrane database of systematic reviews* 2016;**2016**(6):Cd000425.
18. Breitenstein C, Grewe T, Flöel A, et al. Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *Lancet (London, England)* 2017;**389**(10078):1528-38.
19. Doppelbauer L, Mohr B, Dreyer FR, et al. Long-Term Stability of Short-Term Intensive Language-Action Therapy in Chronic Aphasia: A 1-2 year Follow-Up Study. *Neurorehabilitation and neural repair* 2021;**35**(10):861-70.
20. Stahl B, Mohr B, Büscher V, et al. Efficacy of intensive aphasia therapy in patients with chronic stroke: a randomised controlled trial. *J Neurol Neurosurg Psychiatry* 2018;**89**(6):586-92.
21. Elsner B, Kugler J, Pohl M, et al. Transcranial direct current stimulation (tDCS) for improving aphasia in adults with aphasia after stroke. *The Cochrane database of systematic reviews* 2019;**5**(5):Cd009760.
22. Fridriksson J, Rorden C, Elm J, et al. Transcranial Direct Current Stimulation vs Sham Stimulation to Treat Aphasia After Stroke: A Randomized Clinical Trial. *JAMA neurology* 2018;**75**(12):1470-76.
23. Meinzer M, Darkow R, Lindenberg R, et al. Electrical stimulation of the motor cortex enhances treatment outcome in post-stroke aphasia. *Brain : a journal of neurology* 2016;**139**(Pt 4):1152-63.
24. Heikkinen PH, Pulvermüller F, Mäkelä JP, et al. Combining rTMS With Intensive Language-Action Therapy in Chronic Aphasia: A Randomized Controlled Trial. *Frontiers in neuroscience* 2018;**12**:1036.
25. Zheng MX, Hua XY, Feng JT, et al. Trial of Contralateral Seventh Cervical Nerve Transfer for Spastic Arm Paralysis. *The New England journal of medicine* 2018;**378**(1):22-34.
26. Feng J, Li T, Lv M, et al. Reconstruction of paralyzed arm function in patients with hemiplegia through contralateral seventh cervical nerve cross transfer: a multicenter study and real-world practice guidance. *EClinicalMedicine* 2022;**43**:101258.
27. Maas MB, Lev MH, Ay H, et al. The prognosis for aphasia in stroke. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 2012;**21**(5):350-7.
28. Wen-Dong X. Surgical Technique of Xu's CC7 Procedure "Contralateral C7 to C7 Cross Nerve Transfer Through a Trans Longus Colli, Prespinal Route for Treating Spastic Arm". *Operative Neurosurgery* 2020(1):1.
29. Leijnse JN, D'Herde K. Revisiting the segmental organization of the human spinal cord. *Journal of anatomy* 2016;**229**(3):384-93.
30. Takahashi K, Ninomiya T. Morphological changes of dorsal root ganglion cells in the process-forming period. *Prog Neurobiol* 1987;**29**(4):393-410.

31. Zhong LY, Wang AP, Hong L, et al. Microanatomy of the brachial plexus roots and its clinical significance. *Surgical and radiologic anatomy : SRA* 2017;**39**(6):601-10.
32. Gesslbauer B, Hruby LA, Roche AD, et al. Axonal components of nerves innervating the human arm. *Ann Neurol* 2017;**82**(3):396-408.
33. Mille-Hamard L, Bauchet L, Baillet-Derbin C, et al. Estimation of the number and size of female adult rat C4, C5 and C6 dorsal root ganglia (DRG) neurons. *Somatosensory & motor research* 1999;**16**(3):223-8.
34. Cheung RW, Cheung MC, Chan AS. Confrontation naming in Chinese patients with left, right or bilateral brain damage. *Journal of the International Neuropsychological Society : JINS* 2004;**10**(1):46-53.
35. Chen TB, Lin CY, Lin KN, et al. Culture qualitatively but not quantitatively influences performance in the Boston naming test in a chinese-speaking population. *Dementia and geriatric cognitive disorders extra* 2014;**4**(1):86-94.
36. Pike C, Kritzinger A, Pillay B. Social participation in working-age adults with aphasia: an updated systematic review. *Topics in stroke rehabilitation* 2017;**24**(8):627-39.
37. Dosage, Intensity, and Frequency of Language Therapy for Aphasia: A Systematic Review-Based, Individual Participant Data Network Meta-Analysis. *Stroke; a journal of cerebral circulation* 2022;**53**(3):956-67.
38. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet (London, England)* 2019;**394**(10204):1145-58.
39. Fridriksson J, den Ouden DB, Hillis AE, et al. Anatomy of aphasia revisited. *Brain : a journal of neurology* 2018;**141**(3):848-62.
40. Rossi A, Burkhart C, Dell-Kuster S, et al. Serum anticholinergic activity and postoperative cognitive dysfunction in elderly patients. *Anesthesia and analgesia* 2014;**119**(4):947-55.
41. Nousia A, Siokas V, Aretouli E, et al. Beneficial Effect of Multidomain Cognitive Training on the Neuropsychological Performance of Patients with Early-Stage Alzheimer's Disease. *Neural plasticity* 2018;**2018**:2845176.
42. Gu YD, Zhang GM, Chen DS, et al. Seventh cervical nerve root transfer from the contralateral healthy side for treatment of brachial plexus root avulsion. *Journal of hand surgery (Edinburgh, Scotland)* 1992;**17**(5):518-21.
43. Gu Y, Xu J, Chen L, et al. Long term outcome of contralateral C7 transfer: a report of 32 cases. *Chinese medical journal* 2002;**115**(6):866-8.
44. Gu YD. Contralateral C7 root transfer over the last 20 years in China. *Chinese medical journal* 2007;**120**(13):1123-6.
45. Hua XY, Liu B, Qiu YQ, et al. Long-term ongoing cortical remodeling after contralateral C-7 nerve transfer. *Journal of neurosurgery* 2013;**118**(4):725-9.
46. Jiang S, Li ZY, Hua XY, et al. Reorganization in motor cortex after brachial plexus avulsion injury and repair with the contralateral C7 root transfer in rats. *Microsurgery* 2010;**30**(4):314-20.
47. Xu WD, Hua XY, Zheng MX, et al. Contralateral C7 nerve root transfer in treatment of cerebral palsy in a child: case report. *Microsurgery* 2011;**31**(5):404-8.
48. Hua XY, Qiu YQ, Li T, et al. Contralateral peripheral neurotization for hemiplegic upper extremity after central neurologic injury. *Neurosurgery* 2015;**76**(2):187-95; discussion 95.
49. Nardo D, Holland R, Leff AP, et al. Less is more: neural mechanisms underlying anomia treatment in chronic aphasic patients. *Brain : a journal of neurology* 2017;**140**(11):3039-54.
50. Crinion JT, Leff AP. Using functional imaging to understand therapeutic effects in poststroke aphasia. *Current opinion in neurology* 2015;**28**(4):330-7.
51. Kiran S, Meier EL, Johnson JP. Neuroplasticity in Aphasia: A Proposed Framework of Language Recovery. *Journal of speech, language, and hearing research : JSLHR* 2019;**62**(11):3973-85.
52. Hartwigsen G, Saur D. Neuroimaging of stroke recovery from aphasia - Insights into plasticity of the human language network. *Neuroimage* 2019;**190**:14-31.

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

Major research institution	**Name of institutional review board**
Huashan Hospital, Fudan University	Institutional Review Board of Huashan Hospital Affiliated to Fudan University
Sub-centre research institution	**Name of institutional review board**
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
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	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

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
	6b	Explanation for choice of comparators	3-6
Objectives	7	Specific objectives or hypotheses	6, 7
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8,9
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-9
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
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

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8,9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
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
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
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
	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

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14,15
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	NA
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental Material
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065173.R3
Article Type:	Protocol
Date Submitted by the Author:	06-Apr-2023
Complete List of Authors:	Li, Tie; Huashan Hospital Fudan University Department of Hand Surgery Feng, Juntao; Huashan Hospital Fudan University Department of Hand Surgery Hu, Ruiping; Huashan Hospital Fudan University, Department of Rehabilitation Lv, Minzhi; Fudan University, Center of Evidence-Based Medicine, Department of Biostatistics, School of Public Health Chang, Wenshuo; Shanghai International Studies University, Institute of Linguistics Ma, Xingyi; Huashan Hospital Fudan University, Handsurgery Qi, Wenjun; Huashan Hospital Fudan University Zhang, Ying; Shanghai Xuhui Central Hospital, Department of Rehabilitation Chen, Xiuen; Huadong Hospital Affiliated to Fudan University, Department of Rehabilitation Ding, Ling; Shanghai Pudong Hospital, Department of Rehabilitation Gu, Yudong; Huashan Hospital Fudan University Department of Hand Surgery Xu, Wendong; Huashan Hospital Fudan University, Handsurgery
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Surgery
Keywords:	Stroke < NEUROLOGY, Neurosurgery < SURGERY, Clinical trials < THERAPEUTICS

TITLE PAGE

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

Authors:

Tie Li[1-3,7-10†], Juntao Feng[1-3,7-10†], Ruiping Hu[4], Minzhi Lv[6], Wenshuo Chang[5], Xingyi Ma[1,2], Wenjun Qi[1,2], Ying Zhang[11], Xiuen Chen[12], Ling Ding[13], Yudong Gu[1-3,7-10], Wendong Xu[1-3,7-10*]

[1] Department of Hand Surgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China.
[2] Department of Hand and Upper Extremity Surgery, Limb Function Reconstruction Center, Jing'an District Central Hospital, Shanghai, China.
[3] National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University.
[4] Department of Rehabilitation, Huashan Hospital, Shanghai Medical College, Fudan University Shanghai, China.
[5] Institute of Linguistics, Shanghai International Studies University, Shanghai, China.
[6] Center of Evidence-Based Medicine, Department of Biostatistics, School of Public Health, Fudan University, Shanghai, China.
[7] Key Laboratory of Hand Reconstruction, Ministry of Health, Shanghai, China.
[8] Shanghai Key Laboratory of Peripheral Nerve and Microsurgery, Shanghai, China.
[9] State Key Laboratory of Medical Neurobiology, Fudan University, Shanghai, China.
[10] Shanghai Engineering Research Center of Artificial Intelligence Medical Auxiliary Equipment.
[11] Department of Rehabilitation, Shanghai Xuhui Central Hospital, Shanghai, China.
[12] Department of Rehabilitation, Huadong Hospital Affiliated to Fudan University, Shanghai, China.
[13] Department of Rehabilitation, Shanghai Pudong Hospital, Shanghai, China.

†These authors have contributed equally to this work and share first authorship.

***Corresponding Author:**
Prof. Wendong Xu
Email: wendongxu@fudan.edu.cn
Postal address: Department of Handsurgery, Huashan Hospital, Fudan University; No.12 Middle Wulumuqi Rd., Shanghai, China.

Keywords: chronic post-stroke aphasia, C7 neurotomy (NC7) at the intervertebral foramen, intensive speech and language therapy (iSLT), neuroplasticity

Word count: 3889

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.

INTRODUCTION

Background and rationale

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

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

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

We previously developed a surgical procedure for contralateral C7 transfer from the nonparalysed to the paralysed side (contralateral C7 to C7 cross nerve transfer [CC7]), after which patients with stroke demonstrated improved motor function and reduced spasticity in the paralysed arm over 12 months[24]. To data, more than 1,000 patients have undergone this surgery[25]. In addition to arm motor recovery, language improvement was frequently self-reported by patients and caregivers during follow-up, and it occurred very rapidly after CC7 treatment. A few days are by far not sufficient for the transferred C7 nerve to regenerate[26]; therefore, we assumed that the rapid improvement in language function was mediated by the C7 neurotomy (NC7) on the paralysed side (right side), rather than nerve regeneration. During the CC7 operation, we cut the C7 nerve root at the intervertebral foramen to ensure that the C7 nerve on the paralysed side would provide more nerve fibre length[27]. The anterior and posterior roots converge into spinal nerves at the intervertebral foramen, and the posterior roots enlarge near the intervertebral foramen to form

ganglia, also known as the dorsal root ganglion (DRG)[28 29]. The exact location of the neurotomy was the transitional junction of the C7 nerve root with the DRG [30]. The human C7 nerve contains 80,000 fibers[31], 94% of which are sensory fibres emitted by the DRG[32]. Hence, neurotomy of the C7 nerve root at the junction with the DRG could block the ascending sensory pathway from the affected limb to the brain. Based on the anatomy of the brain functional areas, we hypothesized that, since the sensory-motor centre is adjacent to the language centre, if the sensory-motor centre is artificially changed by NC7 at the intervertebral foramen, it maybe possible to stimulate the language centre and achieve relevant functional changes. NC7 may also leads to a change in interhemispheric balance, thus affecting the functional neural circuits of language. We designed this trial to evaluate the surgical effect of NC7 at the intervertebral foramen on the underlying neuroplasticity in patients with chronic post-stroke aphasia. Meanwhile, the iSLT will be used as the control method to assess the effect of the intensive intervention after 3 weeks and the maintenance of the effect after 6 months in both groups. Neuroimaging methods will be simultaneously used to obtain objective data to test our hypothesis.

Aims of the study

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

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

METHODS AND ANALYSIS

Trial design

This study will be a multicentre, randomised, assessor-blinded, active-controlled trial. The participants will be randomly allocated to either group (NC7+iSLT group or iSLT alone group) with a ratio of 1:1 at the four participating centres (Supplemental Table 1). Patients in Group A will be treated with NC7 at the intervertebral foramen combined with 3-week's iSLT, and patients in Group B will be treated with 3-week's iSLT alone. The participants will be recruited from the rehabilitation facilities, outpatient department, or through the collaboration with the Speech Therapy Committee of the Shanghai Association. Eligible patients will be invited to participate in this study and will be asked to sign informed consent.

Eligibility criteria

The inclusion criteria are the following:

1) aphasia for over 12 months after a single onset of infarction or haemorrhage of the left hemisphere, confirmed by magnetic resonance imaging;

2) of 40–65 years, male or female sex, right-handed, native Chinese speakers;

3) Western Aphasia Battery Aphasia Quotient (WAB-AQ) score below 93.8 points;

4) severity score assessed using the BDAE test of level 1 and above;

5) good compliance and ability to cooperate with language rehabilitation training;

6) ability to understand fully and agree with the doctor's treatment plan and sign the informed consent.

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

Exclusion criteria are the following:

1) any surgical contraindication, determined by a qualified anaesthesiologist or clinician;

2) history of aphasia before the last onset of a stroke;

3) serious, untreated mental illness;

4) aphasia due to neurodegenerative diseases or traumatic brain injury;

5) contraindications for EEG and MRI evaluation;

6) inability to complete the assessments and rehabilitation required per study design;

7) severe motor speech disorder and hearing impairment;

8) having received intensive post-stroke rehabilitation therapy 4 weeks before recruitment.

Interventions

NC7 at the intervertebral foramen

A 6-cm long longitudinal incision will be made along the medial border of the sternocleidomastoid muscle on the right side after the cervical plexus, under local /general anaesthesia (depending on the patient's preference and the anaesthesiologist's risk assessment). The structure will be carefully separated layer-by-layer and the brachial plexus will be identified by marking the C7 nerve with a vessel loop. The C7 root will be mobilised and sectioned proximally at the intervertebral foramen. Considering that some patients have limb hemiplegia, CC7 surgery may be required to improve limb function by the end of this trial. Therefore, we will fix the severed C7 root to the fascia, at the junction of the scapulohyoid and sternocleidomastoid muscles, with a silk thread; this will facilitate retrieval and anastomosis with the contralateral C7 root during later CC7 surgical intervention[27].

iSLT Rehabilitation

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

Study setting

This study will begin in July 2022, and the participants will be recruited between July 2022 and July 2023. The study is expected to be completed in July 2024. Fifty patients diagnosed with 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 ± 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±3d post-iSLT onset)**	**Visit 5 (24w±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		√		√	√

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

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

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

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

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

Variable	Measure
Primary outcome	
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 rang is 0–60; higher scores mean better outcomes in naming ability.
Secondary outcome	
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 rand 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.
Surgical safety outcomes	
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.

Adverse events

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

Data collection and management

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

Analyses

Sample size

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

by 5.7 points on average from our literature review[37]. According to results of our phase-I study, the standard deviation was 6.2. With a 2-sided significance level of 0.05, a sample size of 40 patients (20 per group) provided 80% statistical power to demonstrate the difference in the change in BNT scores compared with baseline. Considering a drop-out rate of 20%, 50 patients (25 per group) will recruit.

Statistical analysis

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

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

ETHICS AND DISSEMINATION

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

members of the research team. All procedures will be performed in accordance with the principles of the Declaration of Helsinki.

Patient and public involvement

We asked patients with post-stroke chronic aphasia in rehabilitation facilities for advice on how to meet their physical and emotional needs. The doctors and therapists from the rehabilitation facilities will provide support for the recruitment process. The study results will be disseminated to the public upon completion of the trial and individual test results will be provided to patients upon request.

DISCUSSION

Owing to the high morbidity and heavy disease burden of stroke in China[38], there is an urgent need for effective treatments of chronic post-stroke aphasia. This current manuscript describes the methodology of a trial designed to evaluate the effects of NC7 on language-impairment symptoms in patients with chronic post-stroke aphasia. This study bears major importance because it could provide evidence for the validity of a novel therapeutic strategy for improving language function while attenuating stroke-related dysfunctions.

This study focuses on the evaluation of postoperative language function. Language function can be assessed using naming tests and communication ability assessments, for instance. Patients with aphasia who receive iSLT or non-invasive peripheral stimulation can exhibit improvements in naming ability[39] and social communication[17]; however, the effect sizes are usually modest. In a previous study, we found that the naming ability of patients after CC7 significantly improved, and many other researchers have also used the suitable correct spontaneous naming scores as the only BNT-related index for evaluating language function[40 41]. In this study, we will use the BNT scale as an evaluation index for language function as the primary outcome and the WAB, CADL

Communication Scale, ADL Scale, and Post-Stroke Depression Scale scores as secondary indicators of language repetition, listening comprehension, communication ability, daily life, and psychological status. The ICF speech and language function assessment can detect the degree of changes in voice intonation, oral motor ability, articulation intelligibility, and oral expression to exclude the possible reduction of spasticity after neurotomy for the interference with study results.

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

In conclusion, this will be the first RCT to evaluate the effect of surgery in patients with chronic post-stroke aphasia for whom no effective treatment is available. If found to be efficient, this strategy can be implemented regularly because of its ease of application and low cost. Moreover, larger trials should be extended to other diseases with central nerve injuries to assess the positive effects of this strategy on language and other functions. Once our hypothesis is confirmed, this trial will provide important evidence to support the use of NC7 at the intervertebral foramen as a novel treatment approach for chronic aphasia. A limitation of this study is that it is not double-blind but evaluator-blind, and the experimental group may experience a minor placebo effect. Nevertheless, a secondary endpoint assessment at 6 months post-intervention is scheduled to be conducted to offset the short-term post-surgery placebo effect. At that time, the patient's placebo effect due to invasive interventions will be greatly reduced.

Abbreviations list

RCT = randomised controlled trials; CC7 = contralateral C7 to C7 cross nerve transfer; NC7 = C7 neurotomy; iSLT = intensive speech and language therapy; DRG=dorsal root ganglion; BDAE= Boston Diagnostic Aphasia Examination; BNT = Boston naming test; WAB = Western Aphasia Battery; CADL = Communication Activities of Daily Living; ADL= Activity of Daily Living; ICF=International classification of Functioning, Disability and Health; SADQ-H10= Stroke Aphasic Depression Questionnaire-hospital version; EEG = Electroencephalogram; fMRI = functional magnetic resonance imaging; SAE = Severe Adverse Events.

Competing Interests

None declared.

Patient consent for publication

Not required.

Funding

This work was supported by Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2019-I2M-5-007), Chinese Academy of Medical Sciences Special Project of Clinical and Translational Medicine research cultivating program(2021-I2M-C&T-B-100), National Natural Science Foundation of China (81830063, 82021002) and Shanghai Clinical Research Center for Aging and Medicine (19MC1910500).

Acknowledgements

We would like to thank all the study participants, our colleagues at Huashan Hospital, Fudan University and all the participating institutions.

Contributors

WX is the principal investigator of this study and refined the protocol. TL and JF wrote the manuscript and contributed to the design of the study. ML, the medical statistician for the study, contributed to the statistical design and ethical approval. WC contributed to brain plasticity evaluation design and guidance. YG participated in the concept and design of the study. RH, XM, WQ, YZ, XC, LD have revised the protocol critically for multicentre intellectual content. All authors read and approved the final manuscript.

REFERENCES

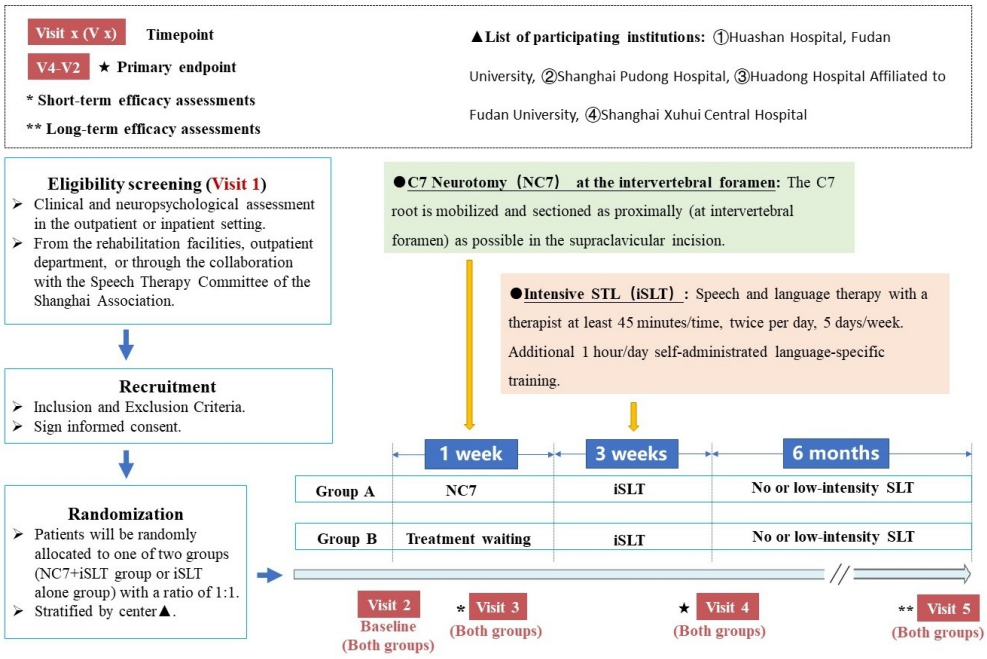
1. Stefaniak JD, Halai AD, Lambon Ralph MA. The neural and neurocomputational bases of recovery from post-stroke aphasia. *Nat Rev Neurol* 2020;**16**(1):43-55.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017;**135**(10):e146-e603.
3. Engelter ST, Gostynski M, Papa S, et al. Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis. *Stroke; a journal of cerebral circulation* 2006;**37**(6):1379-84.
4. Hilari K. The impact of stroke: are people with aphasia different to those without? *Disability and rehabilitation* 2011;**33**(3):211-8.

5. Pollock A, St George B, Fenton M, et al. Top ten research priorities relating to life after stroke. *The Lancet Neurology* 2012;**11**(3):209.
6. Flowers HL, Skoretz SA, Silver FL, et al. Poststroke Aphasia Frequency, Recovery, and Outcomes: A Systematic Review and Meta-Analysis. *Archives of physical medicine and rehabilitation* 2016;**97**(12):2188-201.e8.
7. Bonilha HS, Simpson AN, Ellis C, et al. The one-year attributable cost of post-stroke dysphagia. *Dysphagia* 2014;**29**(5):545-52.
8. Doucet T, Muller F, Verdun-Esquer C, et al. Returning to work after a stroke: a retrospective study at the Physical and Rehabilitation Medicine Center La Tour de Gassies. *Annals of physical and rehabilitation medicine* 2012;**55**(2):112-27.
9. Yagata SA, Yen M, McCarron A, et al. Rapid recovery from aphasia after infarction of Wernicke's area. *Aphasiology* 2017;**31**(8):951-80.
10. Elkana O, Frost R, Kramer U, et al. Cerebral language reorganization in the chronic stage of recovery: a longitudinal fMRI study. *Cortex; a journal devoted to the study of the nervous system and behavior* 2013;**49**(1):71-81.
11. Pedersen PM, Jørgensen HS, Nakayama H, et al. Aphasia in acute stroke: incidence, determinants, and recovery. *Ann Neurol* 1995;**38**(4):659-66.
12. Laska AC, Hellblom A, Murray V, et al. Aphasia in acute stroke and relation to outcome. *Journal of internal medicine* 2001;**249**(5):413-22.
13. El Hachioui H, Visch-Brink EG, de Lau LM, et al. Screening tests for aphasia in patients with stroke: a systematic review. *Journal of neurology* 2017;**264**(2):211-20.
14. Wade DT, Hewer RL, David RM, et al. Aphasia after stroke: natural history and associated deficits. *J Neurol Neurosurg Psychiatry* 1986;**49**(1):11-6.
15. Fridriksson J, Hillis AE. Current Approaches to the Treatment of Post-Stroke Aphasia. *J Stroke* 2021;**23**(2):183-201.
16. Brady MC, Kelly H, Godwin J, et al. Speech and language therapy for aphasia following stroke. *The Cochrane database of systematic reviews* 2016;**2016**(6):Cd000425.
17. Breitenstein C, Grewe T, Flöel A, et al. Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *Lancet* 2017;**389**(10078):1528-38.
18. Doppelbauer L, Mohr B, Dreyer FR, et al. Long-Term Stability of Short-Term Intensive Language-Action Therapy in Chronic Aphasia: A 1-2 year Follow-Up Study. *Neurorehabilitation and neural repair* 2021;**35**(10):861-70.
19. Stahl B, Mohr B, Büscher V, et al. Efficacy of intensive aphasia therapy in patients with chronic stroke: a randomised controlled trial. *J Neurol Neurosurg Psychiatry* 2018;**89**(6):586-92.
20. Elsner B, Kugler J, Pohl M, et al. Transcranial direct current stimulation (tDCS) for improving aphasia in adults with aphasia after stroke. *Cochrane Database Syst Rev* 2019;**5**(5):Cd009760.
21. Fridriksson J, Rorden C, Elm J, et al. Transcranial Direct Current Stimulation vs Sham Stimulation to Treat Aphasia After Stroke: A Randomized Clinical Trial. *JAMA Neurol* 2018;**75**(12):1470-76.
22. Meinzer M, Darkow R, Lindenberg R, et al. Electrical stimulation of the motor cortex enhances treatment outcome in post-stroke aphasia. *Brain : a journal of neurology* 2016;**139**(Pt 4):1152-63.
23. Heikkinen PH, Pulvermüller F, Mäkelä JP, et al. Combining rTMS With Intensive Language-Action Therapy in Chronic Aphasia: A Randomized Controlled Trial. *Frontiers in neuroscience* 2018;**12**:1036.
24. Zheng MX, Hua XY, Feng JT, et al. Trial of Contralateral Seventh Cervical Nerve Transfer for Spastic Arm Paralysis. *The New England journal of medicine* 2018;**378**(1):22-34.
25. Feng J, Li T, Lv M, et al. Reconstruction of paralyzed arm function in patients with hemiplegia through contralateral seventh cervical nerve cross transfer: a multicenter study and real-world practice guidance. *EClinicalMedicine* 2022;**43**:101258.
26. Maas MB, Lev MH, Ay H, et al. The prognosis for aphasia in stroke. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 2012;**21**(5):350-7.
27. Wen-Dong X. Surgical Technique of Xu's CC7 Procedure "Contralateral C7 to C7 Cross Nerve Transfer Through a Trans Longus Colli, Prespinal Route for Treating Spastic Arm". *Operative Neurosurgery* 2020(1):1.
28. Leijnse JN, D'Herde K. Revisiting the segmental organization of the human spinal cord. *Journal of anatomy* 2016;**229**(3):384-93.
29. Takahashi K, Ninomiya T. Morphological changes of dorsal root ganglion cells in the process-forming period. *Prog Neurobiol* 1987;**29**(4):393-410.
30. Zhong LY, Wang AP, Hong L, et al. Microanatomy of the brachial plexus roots and its clinical significance. *Surgical and radiologic anatomy : SRA* 2017;**39**(6):601-10.

31. Gesslbauer B, Hruby LA, Roche AD, et al. Axonal components of nerves innervating the human arm. *Annals of neurology* 2017;**82**(3):396-408.
32. Mille-Hamard L, Bauchet L, Baillet-Derbin C, et al. Estimation of the number and size of female adult rat C4, C5 and C6 dorsal root ganglia (DRG) neurons. *Somatosensory & motor research* 1999;**16**(3):223-8.
33. Cheung RW, Cheung MC, Chan AS. Confrontation naming in Chinese patients with left, right or bilateral brain damage. *Journal of the International Neuropsychological Society : JINS* 2004;**10**(1):46-53.
34. Chen TB, Lin CY, Lin KN, et al. Culture qualitatively but not quantitatively influences performance in the Boston naming test in a chinese-speaking population. *Dementia and geriatric cognitive disorders extra* 2014;**4**(1):86-94.
35. Pike C, Kritzinger A, Pillay B. Social participation in working-age adults with aphasia: an updated systematic review. *Topics in stroke rehabilitation* 2017;**24**(8):627-39.
36. Feng J, Ma X, Hu R, et al. Improvement of language function after C7 neurotomy at the intervertebral foramen in patients with chronic post-stroke aphasia: a phase I cohort study. *medRxiv* 2023:2023.03.22.23287523.
37. Dosage, Intensity, and Frequency of Language Therapy for Aphasia: A Systematic Review-Based, Individual Participant Data Network Meta-Analysis. *Stroke* 2022;**53**(3):956-67.
38. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2019;**394**(10204):1145-58.
39. Fridriksson J, den Ouden DB, Hillis AE, et al. Anatomy of aphasia revisited. *Brain : a journal of neurology* 2018;**141**(3):848-62.
40. Rossi A, Burkhart C, Dell-Kuster S, et al. Serum anticholinergic activity and postoperative cognitive dysfunction in elderly patients. *Anesthesia and analgesia* 2014;**119**(4):947-55.
41. Nousia A, Siokas V, Aretouli E, et al. Beneficial Effect of Multidomain Cognitive Training on the Neuropsychological Performance of Patients with Early-Stage Alzheimer's Disease. *Neural plasticity* 2018;**2018**:2845176.
42. Gu YD, Zhang GM, Chen DS, et al. Seventh cervical nerve root transfer from the contralateral healthy side for treatment of brachial plexus root avulsion. *Journal of hand surgery (Edinburgh, Scotland)* 1992;**17**(5):518-21.
43. Gu Y, Xu J, Chen L, et al. Long term outcome of contralateral C7 transfer: a report of 32 cases. *Chin Med J (Engl)* 2002;**115**(6):866-8.
44. Gu YD. Contralateral C7 root transfer over the last 20 years in China. *Chinese medical journal* 2007;**120**(13):1123-6.
45. Hua XY, Liu B, Qiu YQ, et al. Long-term ongoing cortical remodeling after contralateral C-7 nerve transfer. *Journal of neurosurgery* 2013;**118**(4):725-9.
46. Jiang S, Li ZY, Hua XY, et al. Reorganization in motor cortex after brachial plexus avulsion injury and repair with the contralateral C7 root transfer in rats. *Microsurgery* 2010;**30**(4):314-20.
47. Xu WD, Hua XY, Zheng MX, et al. Contralateral C7 nerve root transfer in treatment of cerebral palsy in a child: case report. *Microsurgery* 2011;**31**(5):404-8.
48. Hua XY, Qiu YQ, Li T, et al. Contralateral peripheral neurotization for hemiplegic upper extremity after central neurologic injury. *Neurosurgery* 2015;**76**(2):187-95; discussion 95.
49. Nardo D, Holland R, Leff AP, et al. Less is more: neural mechanisms underlying anomia treatment in chronic aphasic patients. *Brain : a journal of neurology* 2017;**140**(11):3039-54.
50. Crinion JT, Leff AP. Using functional imaging to understand therapeutic effects in poststroke aphasia. *Current opinion in neurology* 2015;**28**(4):330-7.
51. Kiran S, Meier EL, Johnson JP. Neuroplasticity in Aphasia: A Proposed Framework of Language Recovery. *Journal of speech, language, and hearing research : JSLHR* 2019;**62**(11):3973-85.
52. Hartwigsen G, Saur D. Neuroimaging of stroke recovery from aphasia - Insights into plasticity of the human language network. *Neuroimage* 2019;**190**:14-31.

Figure caption

Figure 1. Trial design in detail and patient flow chart.



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

Major research institution	**Name of institutional review board**
Huashan Hospital, Fudan University	Institutional Review Board of Huashan Hospital Affiliated to Fudan University
Sub-centre research institution	**Name of institutional review board**
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

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	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

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	3-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5, 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7,8
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	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)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-12
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)	8,9

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9-10
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	7-10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
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	12,13
	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

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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13,14
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____NA_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
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_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____16,17____
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_____
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_____
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_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____NA_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Supplemental Material__
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_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.