

Accelerated intermittent theta burst stimulation(iTBS) for the upper limb recovery after subacute stroke(ATLAS): study protocol for a multicenter randomized controlled trial

Hong Yang

the First Affiliated Hospital of Army Medical University

Tian Shu

the First Affiliated Hospital of Army Medical University

Chunyu Duan

the First Affiliated Hospital of Army Medical University

Lin Chen

the First Affiliated Hospital of Army Medical University

Xin Zhang

the First Affiliated Hospital of Army Medical University

Xinyue Xu

the First Affiliated Hospital of Army Medical University

Yiyu Chen

the First Affiliated Hospital of Army Medical University

Han Chen

the First Affiliated Hospital of Army Medical University

Jingming Hou

jingminghou@tmmu.edu.cn

the First Affiliated Hospital of Army Medical University

Study protocol

Keywords: subacute stroke, iTBS, upper limb, randomized controlled trial, multicenter

Posted Date: May 25th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-8784024/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Trials on July 24th, 2026. See the published version at <https://doi.org/10.1186/s13063-026-09857-3>.

Abstract

• **Background:** Stroke is the second leading cause of death globally, with residual upper limb dysfunction being a major contributor to its high disability rate. Currently, there remains a lack of effective rehabilitation approaches to substantially improve upper limb dysfunction. While transcranial magnetic stimulation (TMS) has shown potential in promoting functional reorganization in stroke patients, more effective treatment protocols are still under exploration. In recent years, numerous clinical evidence has indicated that intermittent theta burst stimulation (iTBS) may offer a more efficient pathway for the upper limb recovery after stroke. A few studies have employed accelerated iTBS protocols, preliminarily confirming its safety and efficacy, yet large-sample comparative studies against the standard protocol are lacking. This ATLAS trial aims to compare the effects of accelerated iTBS versus a standard TMS protocol on upper limb recovery and overall functional outcomes in patients with subacute stroke.

• **Methods:** This is a prospective, single-blind, multicenter, randomized controlled clinical trial. A total of 240 patients in the subacute phase of stroke will be recruited from 13 hospitals across 11 cities. Participants will be randomly allocated to either an iTBS group or an low-frequency repetitive TMS (LF-rTMS) group. Both groups will receive treatment five days per week for three consecutive weeks. In addition, all participants will receive standard conventional rehabilitation therapies, including physical agent modalities, therapeutic exercise, occupational therapy, and other commonly used clinical rehabilitation approaches. The primary outcome is the Fugl-Meyer Assessment for Upper Extremity (FMA-UE) evaluated after three weeks of treatment. Secondary outcomes include measures of upper limb function, activities of daily living, clinical disease severity, and neurophysiological indicators assessed by rTMS, evaluated at both post-intervention and after a three-week follow-up period.

• **Discussion:** ATLAS trial is the first multicenter randomized controlled trial to apply an accelerated iTBS protocol to a large cohort of patients with subacute stroke and compare it directly with a standard stimulation protocol. The findings are expected to address the current gap in high-quality evidence regarding the efficacy of accelerated iTBS on upper limb recovery after stroke, thereby promoting the broader clinical adoption of more efficient iTBS-based therapeutic strategies.

• **Trial registration:** Chinese Clinical Trial Registry (ChiCTR2500110766). Registered on Oct 20, 2025.

Structured summary {1b}

Item	Description
Primary Registry and Trial Identifying Number {4}	Chinese Clinical Trial Registry (ChiCTR2500110766) Date registered: Oct 20, 2025
Primary Sponsor and contact information {3b}	Jingming Hou, jingminghou@tmmu.edu.cn
Role of sponsor and funder {3c}	Dr. Jingming Hou, as the principal investigator(PI), is responsible for leading the trial, including defining the research direction, determining the interventions, overseeing trial implementation, providing material, reviewing data and statistical analyses, and guiding manuscript publication. Dr. Hou holds ultimate decision-making authority over all major aspects of this trial, including the determination of the research direction, adjudication of serious adverse events(SAEs), and selection of target journals for study results.
Contact for Public Queries	Hong Yang; yanghong@tmmu.edu.cn
Contact for Scientific Queries	Hong Yang; yanghong@tmmu.edu.cn
Public Title	Accelerated intermittent theta burst stimulation(iTBS) for the upper limb recovery after subacute stroke(ATLAS): study protocol for a randomized controlled multicenter trial
Scientific title	Accelerated intermittent theta burst stimulation(iTBS) for the upper limb recovery after subacute stroke(ATLAS): study protocol for a multicenter randomized controlled trial
Countries of Recruitment	China
Health Condition(s) or Problem(s) Studied	Upper limb function of subacute stroke
Intervention(s)	Accelerated iTBS
Key Inclusion and Exclusion Criteria	Inclusion Criteria 1. Patients clinically diagnosed with first-ever unilateral hemispheric stroke, with MRI or CT confirming hemorrhagic or ischemic stroke, lesion located in one cerebral hemisphere. 2. Age ≥ 18 to ≤ 80 years, any gender. 3. Disease course ≥ 2 weeks and ≤ 6 months. 4. FMA upper limb score < 50. 5. Informed consent obtained from the patient or their guardian.

Exclusion Criteria

1. Brainstem or cerebellar lesions.
2. Severe systemic diseases, cardiac, hepatic, renal diseases, or infectious diseases.
3. History of epilepsy, psychiatric disorders, or other severe emotional dysfunction disorders.
4. Severe cognitive impairment unable to cooperate with assessment and treatment.
5. Intracranial tumors, skull defects, or implants contraindicated for TMS (e.g., cochlear implants, ventriculoperitoneal shunts, etc.).
6. Used drugs that alter cortical excitability within one month (e.g., antiepileptic drugs like levetiracetam, sodium valproate, carbamazepine, oxcarbazepine; antidepressants/anxiolytics like sertraline hydrochloride tablets, escitalopram oxalate tablets, agomelatine tablets, duloxetine hydrochloride enteric-coated capsules, etc.).
7. Modified Ashworth Scale score for biceps muscle tone > 3.
8. Pregnant or lactating women.

Study Type	parallel group, allocation ratio 1:1, single blinding, and superiority trial.
Date of First Enrollment (planned)	01 Nov 2025
Sample Size	240
Primary outcome(s)	The Fugl-Meyer Assessment for Upper Extremity(FMA-UE)
Key Secondary outcome(s)	1. Wolf Motor Function Test (WMFT) 2. Grip Strength 3. Pinch Strength 4. National Institutes of Health Stroke Scale (NIHSS) 5. Modified Barthel Index (MBI) 6. Motor Evoked Potential (MEP) 7. Resting Motor Threshold (RMT)
Ethics Review	Ethics Committee of the First Affiliated Hospital of Army Medical University Approved No. of ethic committee: (A)2025KY190
Individual Trial Participant Data	Do not sharing of deidentified individual clinical trial participant-level data

Introduction

Background and rationale {9a}

Stroke is the second leading cause of death globally, with high incidence and disability rates [1]. The China Stroke Prevention Report [2] shows that the prevalence of stroke among people aged 40 and above in China reaches 12.42 million. The most common dysfunction after stroke is motor dysfunction, and the proportion of upper limb dysfunction is significantly higher than lower limb dysfunction, as high as 80% or more [3]. The severity of upper limb dysfunction is an independent influencing factor for the outcome of activities of daily living after stroke [4]. Once impaired, this function becomes a major barrier to the return of stroke patients to family and societal roles. Therefore, how to effectively promote the recovery of such functions has become a major focus and challenge in rehabilitation training.

Current rehabilitation of hand function after stroke mainly involves comprehensive conventional rehabilitation training such as neurofacilitation, muscle strength training, constraint-induced movement therapy, mirror therapy, and task-oriented training with the assistance of therapists, consuming significant manpower. Even after a certain period and intensity of training, 55%-75% of stroke patients still have upper limb motor dysfunction 3-6 months after onset, and only 30-40% recover partial function by 6 months post-stroke [5]. There is still a lack of methods that can effectively promote functional recovery in stroke patients with upper limb motor dysfunction.

Transcranial magnetic stimulation (TMS), as a non-invasive brain stimulation technique, has been proved its safety and efficacy in the functional recovery of stroke [6]. rTMS can provide repeated, continuous, and large numbers of magnetic stimulation pulses in different patterns, stimulating the cerebral cortex, regulating the excitability of the stimulated area and cortices anatomically connected to it, and adjusting the balance of interhemispheric cortical excitation. Its safety and efficacy have been confirmed in the recovery of motor and swallowing functions in the subacute and chronic phases of stroke. The guidelines on the therapeutic use of repetitive TMS [7] published in 2018 indicate that low-frequency rTMS stimulation of the unaffected M1 area for improving hand motor function in subacute stroke is strongly recommended. Although rTMS has been used clinically for many years [8], the 2024 China Stroke Prevention Report [2] shows that about 75% of stroke patients still have sequelae, and 40% have severe disabilities. Therefore, the exploration of more effective magnetic stimulation protocols still needs to be continuously advanced.

TBS, as a special paradigm of TMS, incorporates burst rhythmic stimulation based on rTMS. It has been widely used in basic and clinical trials since 2005. The TBS stimulation pattern mimics the natural activity of the brain during learning tasks, consisting of 3 pulses of 50Hz in one burst, with an inter-burst frequency of 5Hz, generating 15 pulses per second, totaling 600 pulses. Multiple burst stimulations are equivalent to one train stimulation of conventional rTMS. It includes two modes: iTBS and continuous

TBS (cTBS) [9]. iTBS stimulates for 2 seconds and intermit for 8 seconds, with a total duration of 3 minutes and 20 seconds. iTBS has the potential advantage of achieving better therapeutic efficacy than rTMS with shorter stimulation time, fewer pulses, and lower treatment intensity. Since 2018, it has been approved by the Food and Drug Administration(FDA) for use in people with major depressive disorder [10].

In recent years, many studies have applied iTBS to the treatment research of stroke patients demonstrating its efficacy in motor and cognitive function [11-13]. The iTBS intensity used in these studies was mostly between 70%-100% AMT, 600 pulses once daily, with a total number of sessions between 10-20. However, some studies also applied 1200 pulses [14]. Compared with the traditional 600-pulse protocol, higher-dose novel TBS protocols may yield superior efficacy, a conclusion that remains to be further confirmed. In 2020, the Stanford University team used an accelerated, high-dose, patterned iTBS protocol, significantly shortening the treatment cycle for patients with depression [15]. Meanwhile, another study illustrated that accelerated iTBS seems to produce a more powerful and lasting therapeutic response in patients by providing a higher pulse dose in a shorter time, without increasing the incidence and severity of adverse events(AEs) [16]. Ren et al [17] applied accelerated iTBS to the frontoparietal cognitive network in 41 patients with post-stroke cognitive impairment, revealing its efficacy and safety in treating post-stroke cognitive impairment. The China Rehabilitation Center [18] also recruited 45 stroke patients into accelerated iTBS, cTBS, and sham stimulation groups. The results showed that both iTBS and cTBS led to greater improvement in the FMA-UE score than sham group. However, this study had only 45 cases and lacked a comparative analysis with the established guideline [7]. Considering the insufficient evidence, this ATLAS trial aims to address an existing gap in the using of accelerated iTBS on subacute stroke patients.

Explanation for the choice of comparator {9b}

The guidelines on the therapeutic use of repetitive TMS [7] published in 2018, stated that low-frequency rTMS stimulation of the unaffected primary motor cortex (M1) area is strongly recommended for improving hand motor function in subacute stroke. A recent systematic review [8], encompassing 70 rTMS trials for post-stroke motor recovery, revealed a high degree of consistency in treatment protocols. It found that the M1 was the predominant stimulation target, employed in 58 out of the 70 trials, and that 55 trials utilized a low-frequency paradigm at 1 Hz. To date, there is no high-quality evidence to suggest that accelerated iTBS is superior to this established protocol for motor recovery in subacute stroke.

Objectives {10}

Primary objective

The aim of ATLAS trial is to compare the FMA-UE score of subacute stroke patients randomized to receive the accelerated iTBS and low-frequency rTMS after three- week treatment period.

Secondary objectives

The trial also aims to answer additional research questions related to the overall prognosis of subacute stroke patients, including upper limb function(FMA-UE, WMFT, grip strength, and pinch strength), activities of daily living(MBI), clinical disease severity(NIHSS) and neurophysiological function(MEP and RMT). These assessments will be conducted post-treatment and at a three-week follow-up.

Hypothesis

Compared to low-frequency rTMS, which currently holds the highest level of evidence, accelerated iTBS can significantly improve upper limb motor function in patients with subacute stroke and provide superior overall functional benefits.

Methods: Patient and public involvement, and trial design

Patient and public involvement {11}

In this study, patients with subacute stroke will be recruited from the inpatient departments. Those who met the eligibility criteria will receive a detailed explanation of this study from an investigator and provide written informed consent. All baseline assessments will be completed within three days after consent. Subsequently, a three-week intervention will be initiated, consisting of five daily sessions per week. All post-intervention assessments will be completed within three days after the intervention phase. Following the intervention, there will be a three-week follow-up period during which patients are not permitted to receive any neuromodulation therapy. A final follow-up assessment will be conducted at the end of this period. The schedule for an individual participant is illustrated in Figure1.

Trial design {12}

ATLAS is a prospective, multicenter, single-blind, superiority, randomized controlled trial recruiting in 13 tertiary general hospitals of China.

Methods: Participants, interventions and outcomes

Trial setting {13}

This study will be conducted across 13 tertiary general hospitals located in 11 cities of 5 provinces in China, comprising regions in east, south, and southwest of China.

Characteristics of the people who are needed for the trial

Characteristic	The people we would expect to see included
Age	57.58±16.47
Sex	Male and female
Gender	Man and woman
Race, ethnicity and ancestry	The Han ethnic group and other ethnic minorities in China.
Socioeconomic status	Categorized by educational attainment into: secondary school or below, college, and postgraduate.
Geographic location	The study population is comprised of urban and rural residents from the catchment areas of 13 tertiary general hospitals across 11 cities in 5 provinces of China. Given the relative scarcity of medical and rehabilitation resources in rural China, a substantial proportion of participants are from rural areas.
Other characteristics relevant to the trial	First-ever unilateral ischemic or hemorrhagic stroke, within the subacute to subacute phase (2 weeks to 6 months post-stroke)

Eligibility criteria for participants {14a}

Inclusion criteria are as follows:

- 1.Diagnosed with first-ever unilateral hemispheric stroke, with MRI or CT confirming a unilateral hemorrhagic or ischemic cerebral lesion.
- 2.Age ≥ 18 to ≤ 80 years, male or female
- 3.Duration of illness ≥ 2 weeks and ≤ 6 months.
- 4.FMA-UE score < 50.
- 5.Informed consent obtained from the patient and their guardian.

Exclusion criteria are as follows:

- 1.Brainstem or cerebellar lesions.
- 2.Severe systemic diseases, cardiac, hepatic, renal diseases, or infectious diseases.
- 3.History of epilepsy, psychiatric disorders, or other severe emotional dysfunction disorders.

4. Severe cognitive impairment unable to cooperate with assessment and treatment.
5. Intracranial tumors, skull defects, or implants contraindicated for TMS (e.g., cochlear implants, ventriculoperitoneal shunts, etc.).
6. Use of drugs that alter cortical excitability within one month (e.g., antiepileptic drugs like levetiracetam, sodium valproate, carbamazepine, oxcarbazepine, antidepressants/anxiolytics like sertraline hydrochloride tablets, escitalopram oxalate tablets, agomelatine tablets, duloxetine hydrochloride enteric-coated capsules, etc.).
7. Modified Ashworth Scale score for biceps muscle tone > 3.
8. Pregnant or lactating women.

Eligibility criteria for sites and those delivering interventions {14b}

The study will establish specific qualification criteria for key personnel at each site: the Principal Investigator (PI) at each site must be a physician or therapist engaged in rehabilitation with a senior professional title. The Research Assessor (RA) must include an occupational therapist holding at least an intermediate-level professional title. The Intervention Operator (IO) must be a dedicated magnetic stimulation practitioner (physicians or therapists) with an intermediate-level or higher title.

Who will take informed consent? {32a}

ATLAS has been approved by the ethics committees of all 13 participating sites. The study will fully comply with the code of ethics regarding participant enrollment, study assessment, and data protection. Hospitalized stroke patients at each site will be screened and assessed for eligibility by a trained clinical research team. Once identified as eligible through the screening process, potential participants will be offered enrollment and engaged in a full informed consent procedure.

During the informed consent process, an investigator authorized by PI will communicate the purpose, assessments, procedure, and potential benefits and risks of this study to the participants and their legal guardian in nontechnical language. They will have ample time to decide whether to enroll. Those who choose to participate must sign and date an informed consent form. Enrolled participants may withdraw from the study at any point in time. The original and signed informed consent forms will be retained with the Case Report Form (CRF).

If any changes or amendments to the approved protocol directly affect participants, the informed consent form will be amended accordingly. Participants will be required to resign the revised informed consent form after the same has been approved by the ethical committees of these sites.

Additional consent provisions for collection and use of participant data and biological specimens {32b}

Informed consent will be obtained from at least one legal guardian responsibility before any trial-related procedures begin. Virtual or remote consent (via telephone or video call) will also be acceptable.

Intervention and comparator

Intervention and comparator description {15a}

All participants receive standard rehabilitation therapy. Referring to the Chinese Clinical Management Guidelines for Cerebrovascular Diseases [19], the standard rehabilitation therapy in this trial includes:

1. Physical agent modalities mainly involving medium frequency electrotherapy and biofeedback electrotherapy twice daily, 20 minutes per session.
2. Exercise therapy mainly involving motor relearning techniques, range of motion training for various joints, muscle strength training, core training, balance training and instrument training once daily, 45 minutes per session.
3. Occupational therapy mainly involving activities of daily living training, including eating, dressing, bed-chair transfer, wheelchair control, grooming, once daily, 30 minutes per session.
4. Traditional therapy mainly involving acupuncture, once daily, 40 minutes per session.

Therapists involved in this study have comparable seniority and clinical experience. Accordingly, participants are randomized to receive either accelerated iTBS or LF-rTMS stimulation for five consecutive days a week on three weeks. A transcranial magnetic stimulator with a butterfly coil (Weisi Medical Technology Co., Ltd.) is used for all interventions, following previously reported protocols [18-20]. The details are as follows:

Intervention Group (Accelerated iTBS):Applied to the affected M1 at 90% of the resting motor threshold (RMT). The stimulation is delivered with an intra-burst frequency of 50 Hz and an inter-burst frequency of 5 Hz, totaling 600 pulses. Each burst consists of 3 consecutive pulses. The stimulation pattern involves a 2-second stimulation period followed by an 8-second interval. This cycle will be repeated 3 times per session, with a 15-minute interval between cycles [21], resulting in a cumulative total of 1800 pulses [14].The treatment will be conducted over five consecutive days per week on three weeks.

Control Group (LF-rTMS):Applied to the unaffected M1 at 110% of RMT, frequency 1Hz, delivering 1800 pulses per session over a course of five consecutive days per week on three weeks.

Criteria for discontinuing or modifying allocated intervention/comparator {15b}

1. Participant withdrawal of consent: The intervention will be discontinued if a participant actively requests to withdraw their previously given informed consent for any reason.
2. Investigator judgement for safety: The investigator will discontinue the intervention if, in their medical judgement, continued participation poses a risk to the participant's health, or if the participant's condition deteriorates to a point where continued participation is no longer appropriate.

3. Occurrence of serious adverse events(SAEs): The intervention will be discontinued, and withdrawal from the study will be considered, in the event of a SAE (e.g., epileptic seizure or recurrent stroke) to ensure participant safety.

Strategies to improve adherence to intervention/comparator {15c}

A standardized ATLAS operational manual was established, and all site research teams received comprehensive training with ongoing technical support. To ensure protocol compliance and data integrity, the research team of the principal site will maintain regular communication with all sites through online meetings and on-site visits, supplemented by periodic monitoring. Furthermore, each site is required to maintain a participant research calendar to track scheduled tasks and minimize omissions. To facilitate participation, all study-related assessments and magnetic stimulation sessions are provided free of charge. Finally, an experienced clinical research coordinator (CRC) is designated at each site to oversee the procedural workflow, ensuring each participant completes all assessments and treatment sessions as scheduled.

Concomitant care permitted or prohibited during the trial {15d}

During this trial, participants will be able to receive all standard rehabilitation therapies, with the exception of any neuromodulation therapy .

Ancillary and post-trial care {34}

In the event of a SAE determined to be related to the trial, all necessary examinations and treatments for the SAE will be provided at no cost to the participant. Furthermore, participants retain the right to seek legal compensation for damages. The research team will establish a dedicated mechanism to facilitate long-term follow-up of participants.

Outcomes {16}

Primary outcome

The primary outcome is the standardized FMA-UE score after the three-week intervention. The FMA-UE is a common clinical assessment for post-stroke motor function [22]. It evaluates motor function, sensation, and joint function. Each item is scored as 0 (cannot perform), 1 (partially performs), or 2 (fully performs). The maximum total score for the upper limb and hand is 66.

Secondary outcome

Secondary outcomes include the assessments about the upper limb function, overall function and neurophysiological function of stroke.

1. Wolf Motor Function Test(WMFT) is an internationally recognized scale for assessing upper limb function. It comprises 15 timed functional tasks and 2 strength measures, evaluating a range from simple joint movements to complex actions. For the 15 functional tasks, the time to completion is recorded (capped at 120 seconds), and each is scored on a 0-5 scale. This trial utilized only the performance scores and completion times from the 15 functional tasks, yielding a maximum total score of 75. The WMFT has demonstrated high reliability and validity in assessing patients with moderate to severe upper limb motor impairment [23].
2. Grip strength is measured as a direct method to assess hand muscle strength in stroke patients. Participants grip a handheld dynamometer, which provides an objective measurement. This assessment quantifies the level of hand grip strength, aiding in the evaluation of muscular and neurological recovery.
3. Pinch Strength employs a specialized pinch gauge for a refined assessment of the pinch force generated by the small muscle groups of the thumb and index finger. It provides a specific, quantitative measurement that assists clinicians in objectively evaluating pinch ability.
4. National Institutes of Health Stroke Scale(NIHSS) is a standardized tool for assessing neurological deficits in stroke patients. Widely used in clinical practice and research since its publication in 1989, it quantifies stroke severity across multiple domains: level of consciousness, gaze, visual fields, facial palsy, motor function (upper and lower limbs), limb ataxia, sensation, language, dysarthria, and neglect. Each item is scored from 0 to 2 or higher, yielding a total score ranging from 0 to 42, where higher scores indicate greater neurological impairment [24].
5. Modified Barthel Index(MBI) is an assessment tool for evaluating an individual's performance in activities of daily living (ADLs). It encompasses ten items: grooming, bathing, feeding, toileting, dressing, bowel and bladder control, stair climbing, bed-to-chair transfer, ambulation, and wheelchair use (if applicable). The total score ranges from 0 to 100 points, with scoring bands typically defined as: 0-20 (complete dependence), 21-60 (severe dependence), 61-90 (moderate dependence), 91-99 (mild dependence), and 100 (complete independence).
6. Motor Evoked Potential(MEP) is recorded using TMS, a non-invasive method for assessing the functional integrity of the corticospinal motor pathways. A single magnetic pulse is applied over the M1, which elicits a descending neural volley. This excitation propagates through the corticospinal tract, synapsing at spinal anterior horn cells and ultimately depolarizing peripheral motor nerves, resulting in a recordable compound muscle action potential in the target limb muscles. Key electrophysiological parameters, including latency, amplitude, and central motor conduction time, are measured from the MEP waveforms to evaluate the functional state of the central and peripheral motor pathways.
7. Resting Motor Threshold(RMT) is defined as the minimal stimulus intensity required to elicit a predefined MEP in a target muscle under resting conditions. It serves as a neurophysiological measure of corticospinal excitability. Higher excitability corresponds to a lower RMT; lower excitability corresponds to a higher RMT. There is an inverse relationship between the RMT and MEP.

Harms {17}

In this study, AEs are defined as any untoward medical occurrences following TMS treatment. The overall safety of TMS is well-established [25] . Potential AEs are infrequent and may include transient symptoms such as hearing discomfort or short-term cognitive changes. Extensive research indicates that these symptoms are often not directly attributable to TMS and are typically transient in nature. A SAE of particular concern is the induction of a seizure. However, according to safety guidelines [25], the estimated incidence is exceedingly low (approximately 0.007%). Existing literature suggests that the risk of seizure during TMS is strongly associated with pre-existing conditions such as psychiatric disorders, severe systemic diseases (e.g., cardiac, hepatic, renal), or active infections.

For potential mild AEs such as headache, scalp discomfort, or transient cognitive changes, which typically resolve spontaneously within 1-2 hours, the IO will monitor the participant's condition after each session using a Treatment-Associated Symptom Record Form [26]. To mitigate the risk of SAE like seizures, individuals with a history of epilepsy, psychiatric disorders, other severe emotional/behavioral disorders, major systemic diseases (e.g., cardiac, hepatic, renal), active infections, or recent use of antiepileptic drugs (within one month) were excluded during screening. In the event of any AE that increases in severity or an SAE (e.g., seizure), the IO will immediately initiate emergency procedures, concurrently notifying the responsible physician for specific management. A case review will follow to ensure comprehensive handling. All related medical costs for such events will be covered by the study.

In the event of an AE, the IO must complete an AE report form within 24 hours and notify the PI. The AE must also be reported immediately to relevant clinical departments, the clinical trial management office, and the institutional ethics committee. In urgent situations, an initial oral report may be made to facilitate a rapid response. This must be followed as soon as possible by a detailed written report documenting the event, its impact, and the management measures taken, which is then formally submitted to all concerned parties.

Participant timeline {18}

	Enrolment	Pre-intervention(T_0)	Post-Intervention(T_1)	Follow-up(T_2)
Informed consent	X			
Demographics	X	X		
Stroke history	X	X		
Past medical history	X	X		
Comorbidities	X	X		
Concomitant medications/therapies	X	X		
Drug allergy history	X	X		
FMA-UE	X	X	X	X
WMFT		X	X	X
MBI		X	X	X
NIHSS		X	X	X
Grasp		X	X	X
Pinch		X	X	X
MEP		X	X	X
RMT		X	X	X

Sample size {19}

PASS 15 (NCSS, LLC, Kaysville, Utah, USA) was used to calculate the sample size required for this randomized controlled trial. The intervention group is accelerated iTBS, and the control group is LF-rTMS. The primary outcome measure is FMA-UE. Based on a previous study [27] and pilot-trial results, the mean $\pm$ standard deviation of FMA-UE after intervention in the LF-rTMS group was set at 24.53 ± 6.14 . It is estimated that the FMA-UE score in the accelerated iTBS group could increase by 2.5 points after treatment. Using a two-sided, two-sample variance t-test, with a significance level(α) of 0.050, a sample size of 96 persons per group can achieve 80% power($1-\beta$) to reject the null hypothesis of equal means. Considering a clinical study dropout rate of 20%, this study plans to enroll 240 participants.

Recruitment {20}

Hospitalized stroke patients across all 13 sites will be screened for eligibility by trained clinical research teams. The inpatient bed capacity at these sites ranges from 30 to 100 beds each, with a combined total of nearly 1,000 beds. Approximately 70% of these beds are occupied by stroke patients. To ensure comprehensive enrollment, all centers conduct systematic weekly screenings of all admitted patients.

Assignment of interventions: randomisation

Sequence generation: who will generate the sequence {21a}

In this multicenter RCT study, an Electronic Data Capture (EDC) system will be used to implement a stratified block randomization strategy.

Sequence generation: type of randomisation {21b}

This study employed stratified randomization by center and stroke type (hemorrhagic vs. ischemic) to ensure comparable baseline characteristics between the intervention and control groups within each stratum, thereby enhancing internal validity. Within each stratum, participants were randomized using a block size of 4 with a 1:1 allocation ratio. This block design helps maintain a balanced allocation ratio between groups while mitigating the impact of chance variation on the results.

Allocation concealment mechanism {22}

The centralized randomization module within the EDC system generates and maintains the concealed allocation sequence. Upon researcher entry of a patient's baseline data, the system automatically executes the randomization algorithm and assigns the patient to a study group. To maintain blinding, the allocation result is not revealed at this stage. Instead, the system generates a unique randomization code, which is securely linked to the actual treatment assignment. This code remains concealed and can only be decoded (i.e., the allocation revealed) after the trial database is locked and the formal unblinding procedure is initiated.

Implementation {23}

13 tertiary general hospitals from 5 provinces were selected as study sites based on their extensive research experience and substantial patient resources. Within each center, the randomization process is implemented via the centralized module of the EDC system. This module is managed and monitored by an independent data manager to ensure the integrity, fairness, and unpredictability of the allocation sequence.

Assignment of interventions: blinding

Who will be blinded {24a}

This study employs a single-blind design. The blinding is adhered to by all research personnel except the IO. Specifically, the PI, RA, CRC, and data analysts remain masked to the group allocation throughout the trial.

How will be blinding be achieved {24b}

To minimize the impact of subjective bias and expectancy effects on study outcomes, all personnel involved—including research participants, conventional treatment physicians and therapists, functional assessors, and data managers—are blinded to treatment allocation following stratified block randomization via the EDC system. The IO are the exception, as blinding is not feasible given their direct role in administering the interventions. To mitigate potential bias, IO are required to strictly adhere to the study protocol and are prohibited from disclosing any treatment-related information to blinded personnel. Additionally, IO receive enhanced training and supervision to ensure correct and standardized administration of both active and sham stimulation procedures.

Procedure for unblinding if needed {24c}

Upon completion of all participant interventions and data collection, and following database lock, the study will be unblinded as routine. The treatment allocation codes will be revealed for the final statistical analysis. Emergency unblinding may be required if an SAE occurs and its causality to the intervention needs to be determined for immediate clinical management. The procedure is as follows:

- 1.Immediate Reporting and Preliminary Assessment. The site investigator must immediately report the SAE to the PI and the Ethics Committee. A preliminary assessment of causality and severity must be conducted.
- 2.Formal Application for Emergency Unblinding.If the preliminary assessment indicates that unblinding is necessary to determine causality and guide patient care, the site investigator must submit a formal, written application for emergency unblinding to the PI and the Ethics Committee, detailing the rationale.
- 3.Review, Approval, and Execution.The PI and Ethics Committee will promptly review the application. If approved, a designated, unblinded team member (not involved in the participant's clinical care or assessment) will perform the unblinding. The process must ensure confidentiality and be meticulously documented.
- 4.Documentation and Notification.The details of the unblinding process, the revealed allocation, and the subsequent clinical actions taken must be fully documented in the source documents and the SAE report. The Ethics Committee must be formally notified of the unblinding event and its outcome.
- 5.Post-Unblinding Follow-up.Based on the causality assessment informed by the unblinding, appropriate measures (e.g., treatment modification, enhanced monitoring) will be implemented. The participant's condition will be closely tracked, and all follow-up actions will be recorded.

Data collection and management

Plans for assessment and collection of outcomes {25a}

The ATLAS trial is a pragmatic, clinically embedded study conducted across 13 tertiary hospitals. Outcome data are collected by RA at three time points: pre-intervention (baseline), post-intervention, and follow-up. The same core set of assessments—FMA-UE, WMFT, grip strength, pinch strength, MBI, NIHSS, MEP, and RMT—is administered at each time point. Data are entered directly into the EDC system via electronic CRF, with paper-based CRF maintained as backup. At the baseline assessment only, additional participant information is captured, including demographic characteristics, stroke-related clinical data, and relevant medical history.

Plans to promote participant retention and complete follow-up {25b}

Given the brief in-hospital follow-up period and the completion of all primary and secondary data collection prior to discharge, we anticipate a 100% ascertainment rate for the primary outcome and near-complete follow-up for secondary outcomes. To ensure complete data collection at all three time points, an individualized study calendar was created for each participant. The CRC used this calendar to issue reminders and coordinate all involved personnel for each key assessment, thereby preventing missed visits. For participants discharged before the scheduled follow-up, the CRC provided detailed instructions on follow-up procedures prior to discharge and contacted them to schedule outpatient appointments. These participants returned to complete their follow-up assessments on an outpatient basis, with the assessment process pre-coordinated to allow completion within half a day.

Data management {26}

The EDC system employed in this study ensures data accuracy, completeness, and security through stringent controls governing data collection, entry, review, and transmission. Data entry is performed directly by researchers via electronic CRF. During electronic CRF design, data managers predefine all required data points. The system facilitates real-time data entry, maintains a complete audit trail for all modifications, and preserves source data. Data quality is enforced through automated and manual logic checks. A dedicated data query management module is configured for resolving discrepancies. Source data verification is conducted to confirm accuracy. For data security, all transmissions employ encryption technology to ensure integrity and prevent loss. External data transfers are governed by predefined agreements specifying the method, frequency, and procedures for re-transmission in case of failure, thereby guaranteeing timeliness and completeness.

Confidentiality {33}

All study data will be recorded on CRF. For each completed participant case, the CRF will be promptly retrieved by the CRC and uploaded into the secured EDC system within one month. Access to the live EDC database is strictly restricted to the PI and authorized CRC. For interim statistical analyses, a de-identified dataset will be provided to the independent statistician via a secure, access-controlled institutional portal.

Upon study completion, all participant identifiers will be permanently removed from the final analysis dataset in accordance with regulatory guidelines (e.g., HIPAA principles). The resulting fully de-identified dataset, containing no information that could directly or indirectly identify participants, will be securely archived for future secondary research. All identifiable source documents and data will be destroyed after a predefined retention period. The long-term archival of de-identified data ensures its accessibility beyond the original project timeline.

Statistical methods

Statistical methods for primary and secondary outcomes {27a}

All outcomes will be analyzed using the intention-to-treat (ITT) principle, adhering to the following: randomization, maintain original group assignment, include all participants. Statistics will be performed using SPSS 26.0 (SPSS Inc., Chicago, USA). Conducting preliminary analysis on the basic data of all patients, use the Mann-Whitney test or chi-square test. For the primary outcome before and after intervention, use independent samples t-test or Mann-Whitney U rank sum test. $P < 0.05$ proves the difference is significant, $P < 0.01$ indicates the difference is highly significant. Calculate 95% confidence intervals. For the secondary outcomes, use a two-way mixed-measures ANOVA with factors 2 (between groups: intervention vs. control) $\times$ 3 (time points: initial assessment T0 vs. final assessment T1 vs. follow-up T2). If the sphericity assumption is violated, use Greenhouse-Geisser epsilon correction, and use Bonferroni for post-hoc comparisons. The significance level is $\alpha = 0.05$. As to safety analysis, analyzing the incidence and severity of AEs, it can be determined whether there are safety issues with the treatment intervention, and corresponding measures can be taken.

Who will be included in each analysis {27b}

1. Preliminary Analysis: age, gender, weight, education level, stroke type (hemorrhagic/ischemic), stroke location, stroke course, paralyzed limb (left/right), and pre-intervention assessments etc.

2. Primary Outcome analysis: FMA-UE at post intervention

3. Secondary Outcome analysis: FMA-UE, WMFT, grip strength, pinch strength, NIHSS, MBI, MEP, RMT

4. Safety Analysis: AEs and SAE

How missing data will be handled in the analysis {27c}

The handling of missing data will depend on its proportion. If the percentage of missing data for a given outcome is below a pre-specified threshold of 5%, no imputation will be performed, and the analysis will be conducted on the complete case analysis. If the proportion of missing data exceeds 5%, the Last Observation Carried Forward method will be applied as the primary imputation method. Specifically, for participants with missing values at a given endpoint (e.g., the post-intervention assessment), their most

recent available observation prior to that timepoint (such as a supplementary assessment conducted before hospital discharge) will be carried forward to fill the missing value.

Methods for additional analyses (e.g. subgroup analyses) {27d}

To discern their distinct effects on the findings, a subgroup analysis comparing hemorrhagic and ischemic stroke patients will be performed.

Interim analyses {28b}

Interim analysis was not planned for this trial.

Protocol and statistical analysis plan {5}

Information regarding the trial is publicly available at the Chinese Clinical Trial Registry(www.chictr.org.cn). Participant-level data will not be made available under the conditions of the consent waiver. As such, there is no sharing of participant data possible.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {3d}

The central study team is consist of the chief PI, chief CRC, chief RA, and chief IO based at the First Affiliated Hospital of Army Medical University, Chongqing,China. This team meeting fortnightly is responsible for the trial design, the conduct of the pilot study, and the training of all participating sites. Meanwhile, the PI of each sites are also formed a Trial Steering Committee, meeting twice per year and providing oversight and leadership of this trial. The details of this committee is illustrated below.

Trial Steering Committee	
Porf. Jingming Hou (Principal Investigator)	Department of Rehabilitation, the First Affiliated Hospital of Army Medical University, Chongqing
Porf. Ming Su (Chief Investigator)	Department of Rehabilitation,the Fourth Affiliated Hospital of Soochow University (Suzhou Dushu Lake Hospital), Jiangsu
Porf. Xin Jin (Chief Investigator)	Department of Rehabilitation,Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine, Guangxi
Porf. Yang Mou (Chief Investigator)	Department of Rehabilitation, Chongqing University Fuling Hospital, Chongqing
Prof. Shangqian Wu (Chief Investigator)	Department of Rehabilitation, Guilin Hospital of the Second Xiangya Hospital (Central South University), Guangxi
Prof. Guangquan Xiang (Site Investigator)	Department of Rehabilitation, Chongqing University Renji Hospital (the Fifth Hospital of Chongqing), Chongqing
Prof. Xinyuan Chen (Site Investigator)	Department of Rehabilitation,the First Affiliated Hospital of Fujian Medical University, Fujian
Dr. Xiaokuo He (Site Investigator)	Department of Rehabilitation,the Fifth Hospital Of Xiamen, Fujian
Prof. Kailong Wang (Site Investigator)	Department of Rehabilitation, the First Affiliated Hospital of Guangxi University of Chinese Medicine, Guangxi
Dr. Bin Luo (Site Investigator)	Department of Rehabilitation, the Second People's Hospital of Beihai, Guangxi
Dr. Jianxin Song (Site Investigator)	Department of Rehabilitation, the Second People's Hospital of Nantong, Jiangsu
Dr. Zhonghua Chen (Site Investigator)	Department of Rehabilitation, Maoming People's Hospital, Guangdong
Dr. Zheng Lv (Site Investigator)	Department of Rehabilitation, Longgang Central Hospital of Shenzhen, Shenzhen

Composition of the data monitoring committee, its role and reporting structure {28a}

An independent Data Monitoring Committee (DMC) was constituted prior to study initiation. This committee is responsible for the periodic review (conducted quarterly) of cumulative trial data, overseeing participant safety, monitoring efficacy trends, assessing overall trial conduct quality, and providing recommendations regarding trial design or continuation. The primary mandate of the DMC is to safeguard participant welfare and ensure the scientific integrity and validity of the trial results. The committee comprises four senior clinicians with substantial clinical trial experience, selected from the participating institutions. Additionally, a senior clinician from the principal research center chairs the DMC and is vested with the authority to convene meetings and lead its deliberations.

Frequency and plans for auditing trial conduct {29}

DMC is responsible for reviewing the cumulative data of the clinical trial quarterly, completing safety monitoring, efficacy monitoring, trial operation quality monitoring, trial design adjustment suggestions, etc..During each routine monitoring visit, Source data verification will be performed. For this purpose, the monitor will verify the data entered into the CRF against the original source documents. The source data verification will cover the first three participants enrolled at the site. If a site has enrolled fewer than three participants, it will be performed for all enrolled participants.

Protocol amendments {31}

Any protocol amendments will be submitted for approval by the Ethics Committee of First Affiliated Hospital of Army Medical University, Chongqing, China. Any approved changes will be communicated to PI of all site to obtain site-specific governance approval.

Dissemination policy {8}

The Trial Steering Committee will be responsible for the overall dissemination of trial information. Operational updates and communications will be disseminated to all participating sites via distribution lists and email correspondence. The results of this study will be disseminated through multiple channels to maximize impact. Key findings will be presented at relevant national and international scientific conferences. The primary results, along with a comprehensive statistical analysis, will be submitted for publication in a peer-reviewed medical journal. All publications will adhere to the International Committee of Medical Journal Editors guidelines for authorship.

Discussion

This paper introduces the protocol of the ATLAS trial, a multicenter, single-blind, randomized controlled trial conducted collaboratively by 13 tertiary general hospitals across China. Based on established evidence for iTBS, the trial evaluates an accelerated iTBS protocol as the experimental intervention, with guideline-endorsed LF-rTMS as the active control. ATLAS is designed to address the existing gap in high-quality evidence concerning the effects of accelerated iTBS on post-stroke upper limb recovery.

To ensure scientific rigor and practical feasibility, the coordinating center conducted iterative protocol reviews, a pilot study, and multiple revisions prior to finalizing the design. These steps, complemented by systematic training for all sites, established a robust protocol and implementation pathway. This trial aims to promote the clinical translation of more efficient iTBS paradigms. Its results may inform future updates to clinical guidelines, potentially improving rehabilitation strategies for post-stroke upper-limb dysfunction.

Trial status

The current version of the protocol (version 3.0) was approved by the the Ethics Committee of First Affiliated Hospital of Army Medical University on September 10, 2025, and soon after by the Ethics Committee of other sites. Participant recruitment began on October 31, 2025, with expected completion in December 31, 2027.

Abbreviations

iTBS Intermittent theta burst stimulation

ATLAS Accelerated iTBS for the upper limb recovery after subacute stroke

TMS Transcranial magnetic stimulation

rTMS Repetitive transcranial magnetic stimulation

LF-rTMS Low-frequency repetitive transcranial magnetic stimulation

FMA-UE Fugl-Meyer Assessment for Upper Extremity

WMFT Wolf Motor Function Test

NIHSS National Institutes of Health Stroke Scale

MBI Modified Barthel Index

MEP Motor Evoked Potential

RMT Resting Motor Threshold

cTBS continuous theta burst stimulation

FDA Food and Drug Administration

M1 Primary motor cortex

PI Principal Investigator

RA Research assessor

IO Intervention operator

CRC Clinical research coordinator

CRF Case Report Form

SAE Serious adverse event

AEs Adverse events

DMC Data Monitoring Committee

Declarations

Acknowledgements

The authors are grateful to all the patients and their families for their participation in this trial. We also acknowledge the invaluable contributions of the site investigators, clinicians, research coordinators, and data collection teams. Furthermore, we extend our sincere thanks to the members of the DMC and the Ethics Committee for their diligent oversight and guidance throughout the study, which were essential to ensuring the rigorous conduct of this trial.

Authors' contributions {3a}

HY, co-investigator; study design, trial coordinate, data tabulation, interpretation of data; and draft

ing and revision of final publication. JMH, principal investigator, study concept and design, analysis and interpretation of data, and drafting and revision of final publication. TS, co-investigator, study concept and design, analysis and interpretation of data. CYD, co-investigator, study concept and design, operate the intervention and train for participating sites. LC, co-investigator, study concept and design, train for participating sites. XZ, co-investigator, study assessment, train for participating sites. XYX co-investigator, study assessment, train for participating sites. All authors read and approved the final manuscript for submission. Authorship will follow the agreed trial Authorship and Dissemination Operating Procedure. The authors will include the trial chief investigators plus one individual from each participating site. This may be the site principal investigator or a nominated delegate commensurate with their contribution to the trial. Where journal limitations apply to author number, corporate authorship using the term "and the ATLAS Trial Investigators" may be used to describe this group.

Sources of funding and other support {7a}

ATLAS trial was supported by the Science and Technology Innovation Key R&D Program of Chongqing (No. CSTB2024TIAD-STX0044). The role of the funding body in the design of the study and collection,

analysis, and interpretation of data and in writing the manuscript should be declared.

Availability of data and materials {6}

Anonymized data collected for analysis will be available 6 months after publication of the primary outcome. An application to obtain the data may be made by contacting yanghong@tmmu.edu.cn. No data will be released to a thirdparty representative without written approval by the trial sponsor.

Ethics approval and consent to participate {30}

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Army Medical University, approved No.(A)2025KY190. Furthermore, this protocol had been approved by all Ethics Committees of other 12 participating cites. Written informed consent forms are obtained from all the participants, who can withdraw from the study at any time without giving a particular reason.

Consent for publication

Consent for publication has been included in the trial protocol and approved under the consent waiver. As such, no consent for publication has been obtained from participants.

Competing interests {7b}

The authors declare that they have no competing interests.

Protocol version {2}

Version 3, 03 Sep 2025

References

1. Burden of disease scenarios for 204 countries and territories, 2022-2050: a forecasting analysis for the Global Burden of Disease Study 2021. Lancet (London, England). 2024;403(10440):2204-56. doi: 10.1016/S0140-6736(24)00685-8.
2. Stroke Prevention Project, National Health Commission, Ji Xunming. Brief report on stroke prevention and treatment in China,2024. Journal of Capital Medical University. 2025;46(06):947-60. doi: 10.3969/j.issn.1006-7795.2025.06.001
3. van der Vliet R, Selles RW, Andrinopoulou ER, Nijland R, Ribbers GM, Frens MA, et al. Predicting Upper Limb Motor Impairment Recovery after Stroke: A Mixture Model. Annals of neurology. 2020;87(3):383-93. doi: 10.1002/ana.25679. Epub 2020 Jan 25.
4. Veerbeek JM, Kwakkel G, van Wegen EE, Ket JC, Heymans MW. Early prediction of outcome of activities of daily living after stroke: a systematic review. Stroke. 2011;42(5):1482-8. doi: 10.1161/STROKEAHA.110.604090. Epub 2011 Apr 7.

5. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *The Lancet Neurology*. 2003;2(1):43-53. doi: 10.1016/s1474-4422(03)00266-7.
6. Di Pino G, Pellegrino G, Assenza G, Capone F, Ferreri F, Formica D, et al. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nature reviews Neurology*. 2014;10(10):597-608. doi: 10.1038/nrneurol.2014.162. Epub 2014 Sep 9.
7. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2020;131(2):474-528. doi: 10.1016/j.clinph.2020.02.003.
8. Xie G, Wang T, Deng L, Zhou L, Zheng X, Zhao C, et al. Repetitive transcranial magnetic stimulation for motor function in stroke: a systematic review and meta-analysis of randomized controlled studies. *Systematic reviews*. 2025;14(1):47. doi: 10.1186/s13643-025-02794-3.
9. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005;45(2):201-6. doi: 10.1016/j.neuron.2004.12.033.
10. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet (London, England)*. 2018;391(10131):1683-92. doi: 10.1016/S0140-6736(18)31323-0.
11. Lu J, Huang J, Ye A, Xie C, Bu P, Kang J, et al. Effect of intermittent theta burst stimulation on upper limb function in stroke patients: a systematic review and meta-analysis. *Frontiers in neurology*. 2024;15:1450435. doi: 10.3389/fneur.2024.1450435.
12. Zhang JJ, Bai Z, Mehler DM, Kwong PW, Lam TL, Fong KN. Modulating low-frequency oscillations in post-stroke brains using priming intermittent theta burst stimulation. *European journal of physical and rehabilitation medicine*. 2024;60(4):591-3. doi: 10.23736/S1973-9087.24.08431-4. Epub 2024 Jun 12.
13. Zhang JJ, Sui Y, Sack AT, Bai Z, Kwong PWH, Sanchez Vidana DI, et al. Theta burst stimulation for enhancing upper extremity motor functions after stroke: a systematic review of clinical and mechanistic evidence. *Reviews in the neurosciences*. 2024;35(6):679-95. doi: 10.1515/revneuro-2024-0030.
14. Nettekoven C, Volz LJ, Kutscha M, Pool EM, Rehme AK, Eickhoff SB, et al. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2014;34(20):6849-59. doi: 10.1523/JNEUROSCI.4993-13.2014.
15. Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, et al. Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. *The American journal of psychiatry*. 2020;177(8):716-26. doi: 10.1176/appi.ajp.2019.19070720. Epub 2020 Apr 7.

16. Cole E, O'Sullivan SJ, Tik M, Williams NR. Accelerated Theta Burst Stimulation: Safety, Efficacy, and Future Advancements. *Biological psychiatry*. 2024;95(6):523-35.doi: 10.1016/j.biopsych.2023.12.004.
17. Ren J, Su W, Zhou Y, Han K, Pan R, Duan X, et al. Efficacy and safety of high-dose and personalized TBS on post-stroke cognitive impairment: A randomized controlled trial. *Brain stimulation*. 2025;18(2):249-58. doi: 10.1016/j.brs.2025.02.009. Epub 2025 Feb 18.
18. Tang Z, Huang J, Zhou Y, Ren J, Duan X, Fu X, et al. Efficacy and Safety of High-Dose TBS on Poststroke Upper Extremity Motor Impairment: A Randomized Controlled Trial. *Stroke*. 2024;55(9):2212-20. doi: 10.1161/STROKEAHA.124.046597. Epub 2024 Jul 17.
19. Zhang T, Zhao J, Bai YL, Wang BJ, Qu Y, Li BJ, et al. Chinese Stroke Association Guidelines for Clinical Management of Cerebrovascular Diseases (Second Edition) (Excerpt)—Chapter Eight Cerebrovascular Disease Rehabilitation Management. *Chin J Stroke*. 2023;18(09):1036-48. doi: 10.3969/j.issn.1673-5765.2023.09.010.
20. Struckmann W, Persson J, Gingnell M, Weigl W, Wass C, Bodén R. Unchanged Cognitive Performance and Concurrent Prefrontal Blood Oxygenation After Accelerated Intermittent Theta-Burst Stimulation in Depression: A Sham-Controlled Study. *Frontiers in psychiatry*. 2021;12:659571. doi: 10.3389/fpsy.2021.659571.
21. Tse NY, Goldsworthy MR, Ridding MC, Coxon JP, Fitzgerald PB, Fornito A, et al. The effect of stimulation interval on plasticity following repeated blocks of intermittent theta burst stimulation. *Scientific reports*. 2018;8(1):8526. doi: 10.1038/s41598-018-26791-w.
22. Tauchi Y, Kyougoku M, Okita Y, Takebayashi T. Structural validity and internal consistency of a hypothesized factor structure of the Fugl-Meyer Assessment of the upper extremity. *Topics in stroke rehabilitation*. 2023;30(5):501-11. doi: 10.1080/10749357.2022.2070361. Epub 2022 May 2.
23. Hodics TM, Nakatsuka K, Upreti B, Alex A, Smith PS, Pezzullo JC. Wolf Motor Function Test for characterizing moderate to severe hemiparesis in stroke patients. *Archives of physical medicine and rehabilitation*. 2012;93(11):1963-7. doi: 10.1016/j.apmr.2012.05.002. Epub 2012 May 10.
24. Mistry EA, Yeatts SD, Khatri P, Mistry AM, Detry M, Viele K, et al. National Institutes of Health Stroke Scale as an Outcome in Stroke Research: Value of ANCOVA Over Analyzing Change From Baseline. *Stroke*. 2022;53(4):e150-e5. doi: 10.1161/STROKEAHA.121.034859. Epub 2022 Jan 11.
25. Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmüller J, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clinical neurophysiology*. 2021 Jan;132(1):269-306. doi: 10.1016/j.clinph.2020.10.003. Epub 2020 Oct 24.
26. Liao LY, Zhu Y, Peng QY, Gao Q, Liu L, Wang QH, et al. Intermittent Theta-Burst Stimulation for Stroke: Primary Motor Cortex Versus Cerebellar Stimulation: A Randomized Sham-Controlled Trial. *Stroke*. 2024;55(1):156-65. doi: 10.1161/STROKEAHA.123.044892. Epub 2023 Nov 30.
27. Wu X, Wang R, Wu Q, Liao C, Zhang J, Jiao H, et al. The effects of combined high-frequency repetitive transcranial magnetic stimulation and cervical nerve root magnetic stimulation on upper

Figures

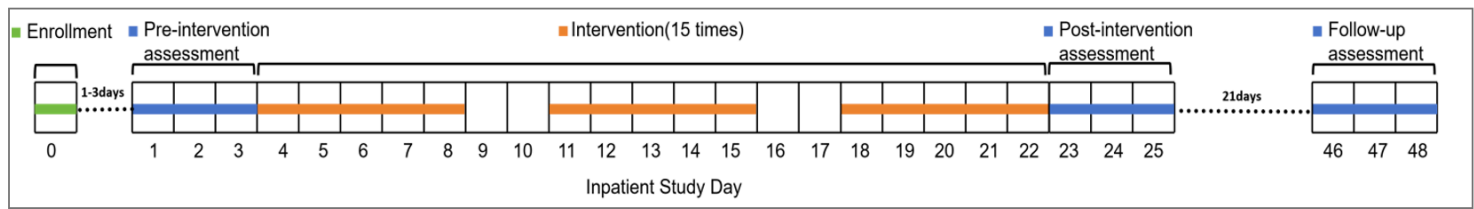


Figure 1

The schedule for an individual participant

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [AppendixB2.sponsorcertificate.pdf](#)
- [AppendixB1.sponsorcertificate.pdf](#)
- [AppendixC2.sponsorcertificateoriginalversion.pdf](#)
- [AppendixA.ethicalapproval.pdf](#)
- [AppendixC1.sponsorcertificateoriginalversion.pdf](#)