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Study on the Effects of Pharmacological and Physical Therapy in Delaying the Progression of Moyamoya Disease (Moyamoya Syndrome)

Randomized Controlled Study

Clinical Research Protocol

Affiliated project: Research on Early Warning Technologies and Precision Treatment Strategies for Moyamoya Disease (Moyamoya Syndrome)

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Commissioning organization: National Health Commission Medical and Health Science and Technology Development Research Center

Implementing institution: Beijing Tiantan Hospital, Capital Medical University

Lead institution: Beijing Tiantan Hospital, Capital Medical University

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Protocol Synopsis

Project Name	Study on the Effects of Pharmacological and Physical Therapy in Delaying the Progression of Moyamoya Disease (Moyamoya Syndrome)
Study Objective	To explore whether aspirin pharmacological therapy and physical therapy can delay the progression of moyamoya disease (moyamoya syndrome).
Study Design	Multicenter, prospective, 2 x 2 factorial, randomized, double-blind, blinded-endpoint clinical study
Total Number of Cases	724 cases

Case Selection	*Inclusion criteria* *1) 18 <= age <= 70 years;* *2) Diagnosed with moyamoya disease or moyamoya syndrome by cerebral angiography or MRA;* *3) No symptomatic stroke, including ischemic or hemorrhagic stroke, before completion of randomization after enrollment;* *4) No prior cerebral revascularization surgery of any form, including multiple burr holes, EDAS, and STA-MCA, before enrollment;* *5) No clear surgical indication, or the patient refuses surgical treatment for personal reasons and requests conservative treatment;* *6) Signed informed consent form.*
	Exclusion criteria *1) Previous history of any form of intracranial hemorrhage, such as subarachnoid hemorrhage, intracerebral hemorrhage, or intraventricular hemorrhage; history of symptomatic ischemic stroke; frequent TIA attacks*

	before enrollment, defined as 3 or more attacks within 7 days; or history of epileptic seizures; *2) Concomitant cerebrovascular diseases that may significantly affect perioperative risk or outcome assessment, such as intracranial aneurysm, cerebral arteriovenous malformation, or arteriovenous fistula requiring concurrent treatment;* *3) Previous history of severe craniocerebral trauma, brain tumor, encephalitis, meningitis or other central nervous system inflammation, other major craniocerebral disease, any form of invasive brain treatment, or radiotherapy;* *4) Planned cerebral revascularization surgery within 3 months;* *5) Severe cardiac dysfunction (ejection fraction < 50% or NYHA class III-IV heart function), hepatic dysfunction (ALT or AST > 2 times the upper limit of normal), or renal insufficiency (serum creatinine > 3 mg/dL); concomitant major systemic disease, such as a history of unstable angina, acute coronary syndrome, asthma, or COPD; severe non-cardiovascular comorbidity with expected survival < 1 year; or other severe comorbidity that the investigator judges would significantly increase study risk;* *6) Contraindication to aspirin:* *a. Known allergy;* *b. Severe renal insufficiency (creatinine > 1.5 times the upper limit of normal)*

	or severe hepatic insufficiency (ALT or AST > 2 times the upper limit of normal); *c. Severe heart failure (NYHA class III-IV);* *d. Coagulation disorder or history of systemic bleeding;* *e. History of thrombocytopenia or neutropenia;* *f. History of drug-induced hematological disease or liver function injury;* *g. White blood cell count < 2 x 10^9/L or platelet count < 100 x 10^9/L;* *h. History of gastrointestinal bleeding within 3 months before enrollment, or definite history of gastric ulcer or gastritis;* *i. Other contraindications to aspirin.* *7) Contraindication to ischemic conditioning:* *a. Concomitant peripheral vascular disease of the upper or lower limbs, especially significant stenosis or occlusion of the brachial artery or the ulnar or radial artery, or a condition judged by the investigator to be unsuitable for upper-arm cuff compression to implement remote ischemic treatment;* *b. Conditions that may affect the safety of upper-limb RIC, including but not limited to severe skin or soft-tissue infection/damage, obvious lymphedema, arteriovenous fistula or dialysis fistula, recent deep venous thrombosis, or investigator judgment that the patient cannot tolerate upper-arm cuff compression;*

	c. Known history of allergy to the RIC device or its component materials; *8) Need for aspirin and/or antiplatelet drugs because of diseases other than moyamoya disease, or continuous use of other antiplatelet drugs for >= 5 days before enrollment with the last dose <= 10 days before enrollment;* *9) Need for anticoagulant therapy, or use of heparin or oral anticoagulants within 10 days before enrollment;* *10) Pregnant women, suspected pregnancy, or lactating women;* *11) Conditions affecting completion of key follow-up assessments;* *12) Current participation in another interventional clinical trial where the investigator considers that it may interfere with outcome assessment.*

	Withdrawal criteria: *1) Participation in another interventional clinical trial before completion of this study, where the investigator considers that it may interfere with outcome assessment;* *2) Loss to follow-up: after reasonable follow-up efforts, the subject still cannot be contacted, or the subject clearly refuses further follow-up, resulting in inability to obtain key clinical outcome information within the prespecified time window;* *3) Serious violation of the study protocol for any reason during follow-up;* *4) The subject or the subject's legal representative withdraws informed consent and clearly requests withdrawal from the study, including refusal of further follow-up;* *5) A serious adverse event occurs and the investigator judges that continued participation in the study or continued RIC intervention may increase the subject's risk;*

	6) Unblinding occurs for any reason during the study. *Note: If the subject stops RIC intervention but agrees to continue follow-up and outcome assessment, this is not considered withdrawal from the study. Follow-up should be completed as far as possible, and the subject should be included in the primary analysis according to the ITT principle.*
Treatment Regimen	After randomization, all patients will be divided into four groups: control group (aspirin placebo + sham ischemic conditioning procedure); intervention group 1 (aspirin treatment + sham ischemic conditioning procedure); intervention group 2 (aspirin placebo + ischemic conditioning); and intervention group 3 (aspirin treatment + ischemic conditioning). All patients will begin pharmacological intervention and ischemic conditioning intervention within 24 hours after randomization. Pharmacological intervention Aspirin or placebo will be taken orally every morning for 1 year. To ensure medication adherence, study drugs will be dispensed and regularly recovered for pill counting. Aspirin: 100 mg, orally on an empty stomach in the morning, once daily; Placebo: consistent with aspirin in dosage form, dose, packaging, and appearance; 100 mg, orally on an empty stomach in the morning, once daily. Ischemic conditioning intervention

	The first 3 months after randomization will be the intensive phase, during which ischemic conditioning or sham procedure treatment will be completed once daily. Months 4 to 6 after randomization will be the maintenance phase, during which ischemic conditioning or sham procedure treatment will be completed no fewer than 4 times per week, with a maximum of once per day. Real ischemic conditioning procedure group: the ischemic conditioning device will be used once daily, including 5 treatment cycles. After blood pressure is measured in both arms, the upper limit of the bilaterally measured blood pressure will be used as the inflation value. The cuffs on both upper limbs will be inflated and maintained for 5 minutes, followed by deflation for 5 minutes. Each treatment session will last 45 minutes. Sham ischemic conditioning procedure group: the sham ischemic conditioning device will be used once daily, including 5 treatment cycles. The cuffs on both upper limbs will be inflated to 60 mmHg and maintained for 5 minutes, followed by deflation for 5 minutes. Each treatment session will last 45 minutes. Intervention discontinuation If a patient experiences a safety endpoint event, other bleeding event, ASA-related adverse reaction, or RIC-related adverse reaction, medication may be suspended or discontinued, and management will be provided according to the emergency treatment plan.

Efficacy Assessment	*Efficacy evaluation indicators (primary and secondary efficacy indicators)* *Primary endpoint events:* *(1) The primary efficacy endpoint event is disease progression or the occurrence of a cerebrovascular event within 1 year, including transient ischemic attack and cerebral infarction.* *(2) The safety endpoint event is severe or moderate bleeding within 1 year, as defined by GUSTO, or limb soft-tissue injury, peripheral vascular injury, or deep venous thrombosis related to ischemic conditioning within 1 year.* *Secondary endpoint events:* *(1) New vascular events within 1 year, including transient ischemic attack, cerebral infarction, cerebral hemorrhage, myocardial infarction, and vascular death; each new vascular event will also be evaluated independently;* *(2) Disabling stroke events within 1 year (mRS score > 1);* *(3) Occurrence and severity of stroke or transient ischemic attack at 3 months and 1 year; severity will be classified according to an ordered 6-level scale combined with the mRS: fatal stroke / severe nonfatal stroke [mRS 4 or 5] / severe nonfatal stroke [mRS 4 or 5] / moderate stroke [mRS 2 or 3] / mild stroke [mRS 0 or 1] / TIA / no stroke-TIA;* *(4) Change in neurological deficit at 3 months, compared with baseline, based on the change in mRS score at the 3-month follow-up;* *(5) Quality of life at the 3-month and 1-year follow-up visits, assessed using the EQ-5D-5L scale.*

	(6) Average monthly frequency of TIA attacks within 1 year. *(7) Progression of white matter hyperintensity (WMH) lesions within 1 year.*
Statistical Methods	1. Statistical methods for baseline data analysis: Descriptive statistics: continuous variables, such as age and blood pressure, will be expressed as mean +/- standard deviation or median (interquartile range), and categorical variables, such as sex and comorbidities, will be expressed as frequencies and percentages. Between-group balance testing: analysis of variance or the Kruskal-Wallis test will be used for continuous variables, and the chi-square test or Fisher's exact test will be used for categorical variables, to assess whether baseline characteristics are comparable across groups after randomization. 2. Statistical methods for endpoint events: Survival analysis: the Kaplan-Meier method will be used to estimate event rates in each group and plot survival curves. Between-group comparisons will be performed using the Log-rank test.

	Multivariable analysis: a Cox proportional hazards model will be used, with treatment group as the independent variable and with adjustment for center as a stratification factor and other baseline covariates that may affect prognosis. Hazard ratios (HRs) and 95% confidence intervals will be calculated. Logistic regression model: for binary variables, center and baseline covariates will be adjusted for, and odds ratios (ORs) and 95% CIs will be calculated. For ordinal categories, ordinal logistic regression or nonparametric tests may be used. For continuous variables, ANCOVA or mixed linear models may be used. Multiple comparisons: pairwise comparisons among the four groups will be performed while controlling type I error. Bonferroni correction or Dunnett's test may be used. Intention-to-treat analysis (ITT): the primary analysis will be based on the ITT principle. Missing data will be handled using appropriate methods, such as multiple imputation or last observation carried forward. Per-protocol analysis set (PP): as a sensitivity analysis, only patients who complete follow-up and have good adherence will be included.

Study Duration	Period for each patient From signing the informed consent form to 1 year (12 months) after enrollment. Overall study implementation period Patient enrollment period: within 3 years from the date of protocol approval (March 1, 2026 - February 28, 2029). Patient study period: from the date of protocol approval to the date specified in "Termination of This Study." Interim follow-up: performed when one half of the total sample size has completed follow-up;

Abbreviations

Abbreviation	Full English Name	Chinese Full Name
MMD	Moyamoya disease	Moyamoya disease

MMS	Moyamoya syndrome	Moyamoya syndrome
ASA	Aspirin	Aspirin
RIC	Remote Ischemic Conditioning	Remote ischemic conditioning
TIA	Transient Ischemic Attack	Transient ischemic attack
mRS	Modified Rankin Scale	Modified Rankin Scale for stroke
WMH	White Matter Hyperintensities	White matter hyperintensities
EDC	Electronic Data Capture System	Electronic data capture system

I. Research Background

Moyamoya disease (MMD) is a chronic occlusive cerebrovascular disease characterized by progressive stenosis or occlusion at the terminal portion of the internal carotid artery, with formation of an

abnormal vascular network at the base of the brain. Moyamoya syndrome (MMS) has the same cerebrovascular imaging and clinical manifestations as moyamoya disease, but it is accompanied by other systemic comorbidities. Moyamoya disease and moyamoya syndrome are collectively referred to as moyamoya-like cerebrovascular disease. They are highly prevalent in East Asia, and China has a large patient population. In 2018, the incidence was 1.6 per 100,000 person-years, and the disease is a major cause of stroke in children, adolescents, and young adults [1]. This group of diseases often causes severe complications such as stroke and cognitive impairment, leading to poor prognosis and reduced ability to live independently [2]. Among patients who do not receive effective treatment, the risk of severe neurological deficit or death is as high as 75%, and approximately 60% of patients with moyamoya disease develop cognitive impairment [3]. Therefore, moyamoya disease (moyamoya syndrome) is a major health problem that seriously affects the health of the Chinese population.

At present, several urgent problems remain in the clinical diagnosis and treatment of moyamoya disease (moyamoya syndrome). First, the epidemiological characteristics and disease susceptibility of this condition in the Chinese population are not yet fully clear. Second, reliable clinical assessment tools and standardized risk prediction models for moyamoya disease are lacking, and there is still no clear basis for identifying which patients need timely intervention. Third, a systematic precision treatment pathway for moyamoya disease has not yet been established, and high-quality evidence is still lacking regarding the role of pharmacological and physical therapy in delaying disease progression. Therefore, systematic research to clarify the

efficacy of different treatment approaches in moyamoya disease is of great significance for promoting the establishment of an integrated diagnostic and therapeutic system for this disease.

[Add a paragraph introducing ischemic conditioning and its role in stroke and MMD.]

Systematic treatment is an important means to improve the prognosis of moyamoya disease. Current major treatment options include revascularization surgery and pharmacological therapy. Previous studies have shown that revascularization surgery can improve cerebral blood flow and reduce the risk of stroke; however, for asymptomatic or early-stage patients, surgery is not the only option [4]. In terms of pharmacological therapy, nonsurgical treatments such as antiplatelet therapy and intensive lipid-lowering therapy may delay disease progression, but high-quality clinical evidence remains lacking. In addition, emerging physical therapies such as ischemic conditioning have been shown to improve the tolerance of brain tissue to ischemia and have demonstrated potential therapeutic value in patients with stroke [5]. However, the safety and efficacy of these treatment approaches in patients with moyamoya disease require further study and validation.

Therefore, this study proposes to conduct a multicenter, prospective randomized controlled clinical trial to systematically evaluate the efficacy and safety of aspirin therapy and ischemic conditioning therapy in delaying the progression of moyamoya disease, and to provide evidence-based support for nonsurgical treatment strategies for patients with moyamoya disease.

[The following content was moved from the study rationale section

and should be integrated with the research background.]

Even when patients with moyamoya disease (moyamoya syndrome) have not yet developed definite symptoms of cerebral infarction, their cerebral hemodynamics may already be in a compensated or critical state. They are often prone to nonspecific symptoms such as headache and dizziness, subjective cognitive decline, and TIA attacks, and they have a potential risk of progression to symptomatic stroke. Microembolus formation and vascular endothelial dysfunction may further reduce flow reserve and aggravate hypoperfusion, thereby leading to adverse events. For such mildly affected patients, early intervention has important clinical value for delaying disease progression and preventing cerebrovascular events.

Aspirin irreversibly inhibits cyclooxygenase-1 and blocks thromboxane A2 production, thereby inhibiting platelet aggregation. In the pathological process of moyamoya disease (moyamoya syndrome), microcirculatory changes and vascular intimal injury may activate platelets and promote microthrombus formation, which may aggravate ischemia-induced stroke. Therefore, aspirin may reduce the risk of ischemic events by inhibiting platelet aggregation. Ischemic conditioning is a noninvasive physical therapy that activates systemic endogenous protective mechanisms through transient limb ischemia-reperfusion, such as improving endothelial function, promoting collateral circulation, and upregulating antioxidant factors. It may enhance the tolerance of brain tissue to ischemia, improve cerebral blood flow reserve, and thereby delay disease progression. The combined use of the two interventions may produce a synergistic effect.

(2) Basis for determination:

① Patients with moyamoya disease are at high risk of cerebrovascular events, and their annual stroke incidence is significantly higher than that of the general population. Previous observational studies have shown that long-term aspirin use can reduce the risk of recurrent ischemic stroke in patients with moyamoya disease without

significantly increasing bleeding risk.

② Research basis for ischemic conditioning in cerebrovascular disease: pilot studies, such as RIC studies, suggest that ischemic conditioning can improve cerebral perfusion in patients with symptomatic intracranial arterial stenosis and reduce the frequency of TIA attacks. Preliminary studies of RIC efficacy in adult and pediatric moyamoya disease also indicate that ischemic conditioning can improve cerebral blood flow reserve and has a favorable safety profile.

II. Study Objectives

To investigate whether aspirin and ischemic conditioning, either alone or in combination, can delay clinical progression and prevent ischemic attacks in patients with mild moyamoya disease and moyamoya syndrome.

III. Study Design and Protocol

3.1 Study Design

A multicenter, prospective, 2 x 2 factorial, randomized, double-blind, blinded-endpoint clinical study.

Rationale for the design:

The purpose of this randomized controlled study is to verify the efficacy and safety of oral aspirin and ischemic conditioning in delaying the progression of moyamoya disease and preventing ischemic attacks, and to analyze whether the combined application of the two interventions is superior to either intervention alone. Therefore, the above design is adopted.

3.2 Sample Size and Grouping

3.2.1 Target sample size and grouping

A total of 724 patients are planned for enrollment and will be divided into four groups:

Aspirin + ischemic conditioning group: 181 cases

Aspirin + sham ischemic conditioning group: 181 cases

Placebo + ischemic conditioning group: 181 cases

Placebo + sham ischemic conditioning group: 181 cases

3.2.2 Basis for target sample size determination

The sample size was calculated using R. The sample size calculation for this study is based on a 2 x 2 factorial randomized controlled trial design. The interaction between the two interventions, aspirin and ischemic conditioning, will be tested first. If the interaction is not significant, the main analysis will focus on the respective main effects. Based on preliminary data from the study team, the endpoint event rate is 15% in the control group, 7% in the aspirin treatment group, and 8% in the ischemic conditioning

treatment group. Patients will be randomized to the four groups in a 1:1:1:1 ratio. The significance level (alpha) is set at 0.05 (two-sided test), and the statistical power (1-beta) is set at 80%. The calculation indicates that 650 patients are required (162.5 cases per group?). Considering an approximately 10% nonadherence rate during follow-up, the required sample size is 724 patients (181 cases per group), which meets the statistical requirements.

3.3 Follow-up Plan and Content

3.3.1 Follow-up plan

Enrolled subjects will receive three visits in total: a telephone follow-up at 3 months (+/- 7 days) [follow-up time point 1]; a telephone follow-up at 6 months (+/- 7 days) [follow-up time point 2]; and an outpatient follow-up at 12 months (+/- 15 days) [follow-up time point 3], during which brain MRI (T1 + T2 + DWI + FLAIR) + MRA will be completed.

In addition, patients will receive a visit if new neurological symptoms or suspected events occur, including worsening of the original ischemic event or the occurrence of new transient or persistent neurological symptoms. The subcenter shall submit the event within 96 hours after its occurrence and provide materials for interpretation.

3.3.2 Follow-up content

Follow-up time points 1 and 2: telephone follow-up

1) New or recurrent neurological symptoms, including TIA, cerebral infarction, and cerebral hemorrhage (time of occurrence, frequency, treatment, imaging data, and cause of bleeding), adverse events and safety events (including intracranial hemorrhage and other bleeding events possibly related to aspirin, adverse drug reactions, limb discomfort related to ischemic conditioning, venous thrombosis, etc.);

2) Neurological function score, assessed using the mRS;

3) Quality-of-life score, assessed using the EQ-5D-5L scale;

4) Intervention adherence;

Follow-up time point 3: outpatient visit:

Including the contents of the telephone follow-up, as well as brain MRI (T1 + T2 + DWI + FLAIR) + MRA.

If a patient cannot complete the follow-up examination at a medical center involved in this study, the patient will be required to complete MRI + MRA at a local hospital (secondary grade A hospital or above). The investigators will ask the patient's family members to upload the follow-up data and will evaluate its quality. If the above data do not meet the required quality standard or if further details cannot be obtained, the patient will be withdrawn from follow-up.

3.4 Study Period

3.4.1 Period for each patient

From signing the informed consent form to 1 year (12 months) after enrollment.

3.4.2 Overall study implementation period

Patient enrollment period: within 3 years from the date of protocol approval (March 1, 2026 - February 28, 2029).

Patient study period: from the date of protocol approval to the date specified in "Termination of This Study."

IV. Study Endpoints

4.1 Primary Endpoint Events

(1) The primary efficacy endpoint event is disease progression or the occurrence of a cerebrovascular event within 1 year, including transient ischemic attack and cerebral infarction.

(2) The safety endpoint event is severe or moderate bleeding within 1 year, as defined by GUSTO, or peripheral vascular injury or deep venous thrombosis related to ischemic conditioning within 1 year.

4.2 Secondary Endpoint Events

(1) New vascular events within 1 year, mainly including transient ischemic attack, cerebral infarction, cerebral hemorrhage, myocardial infarction, and vascular death; each new vascular event will also be evaluated independently;

(2) Disease progression within 1 year;

(3) Progression of white matter hyperintensity (WMH) lesions within 1 year;

(4) Disabling stroke events within 1 year (mRS score > 1);

(5) Occurrence and severity of stroke or transient ischemic attack within 6 months and 1 year. Severity will be classified according to an ordered 6-level scale combined with the mRS: fatal stroke / severe nonfatal stroke [mRS 4 or 5] / severe nonfatal stroke [mRS 4 or 5] / moderate stroke [mRS 2 or 3] / mild stroke [mRS 0 or 1] / TIA / no stroke-TIA;

(6) Change in neurological deficit at 3 months, compared with baseline, based on the change in mRS score at the 3-month follow-up;

(7) Quality of life at the 3-month and 1-year follow-up visits, assessed using the EQ-5D-5L scale;

(8) Average monthly frequency of TIA attacks within 1 year.

4.3 Event Definitions

(1) Disease progression: MRA findings during follow-up through study completion that meet any of the following criteria: weakening or disappearance of the blood flow signal at the terminal internal carotid artery, middle cerebral artery, anterior cerebral artery, or posterior cerebral artery compared with baseline; extension of the range of stenotic or occlusive lesions compared with baseline; or progression of a stenotic lesion to an occlusive lesion compared with baseline.

(2) Cerebrovascular events:

Transient ischemic attack: a neurological deficit caused by sudden focal cerebral ischemia that completely resolves, lasts less than 24 hours, and shows no evidence of new cerebral infarction on imaging examination (CT and/or MR). Other non-ischemic causes, such as brain infection, brain trauma, brain tumor, epilepsy, severe metabolic disease, or degenerative neurological disease, must be excluded.

Cerebral infarction: acute focal cerebral infarction. Criteria: (1) clinical signs or imaging evidence of a new focal neurological deficit with acute onset lasting more than 24 hours, after excluding other non-ischemic causes such as brain infection, brain trauma, brain tumor, epilepsy, severe metabolic disease, or degenerative neurological disease; or (2) an acute cerebral ischemic event, after excluding other non-ischemic causes, with focal symptoms or signs lasting less than 24 hours but accompanied by imaging evidence of a new infarct lesion; or (3) progression of a pre-existing vascular ischemic stroke, defined as an increase in NIHSS score of at least 4 on the basis of the primary ischemic stroke, excluding hemorrhagic transformation after infarction or symptomatic intracranial hemorrhage, lasting more than 24 hours and accompanied by new ischemic changes on brain MRI or CT. Etiological classification will be performed according to the TOAST criteria. Cerebral hemorrhage: hemorrhagic stroke is defined as acute focal, global cerebral, or spinal neurological dysfunction caused by

nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

(3) Progression of white matter hyperintensity lesions: progression of WMH lesions will be assessed using a modified visual WMH rating scale. The scale has four grades: Grade A, no lesions; Grade B, deep WMH diameter >= 3 mm or periventricular hyperintensity >= 5 mm; Grade C, 1-10 deep WMHs with a diameter of 4-10 mm or periventricular hyperintensity with a diameter of 6-10 mm; Grade D, more than 10 deep WMHs with a diameter of 4-10 mm, confluent deep WMH lesions, or periventricular hyperintensity diameter >= 11 mm. During follow-up, an increase in the number or diameter of WMH lesions on the same imaging level, or an increase in grade compared with baseline, is defined as lesion progression.

V. Subject Selection

5.1 Target Patient Population

Patients with mild moyamoya disease who are clinically diagnosed with moyamoya disease or moyamoya syndrome, have no history of symptomatic stroke, and have no frequent TIA (> 2 times/month). Enrolled patients must meet all requirements in "5.4.1.2 Inclusion Criteria" and must not meet any item in "5.4.1.3 Exclusion Criteria."

5.2 Inclusion Criteria

1) 18 <= age <= 70 years;

2) Diagnosed with moyamoya disease or moyamoya syndrome by cerebral angiography or MRA;

3) No symptomatic stroke, including ischemic or hemorrhagic stroke, before completion of randomization after enrollment; specifically including the following situations:

4) No prior cerebral revascularization surgery of any form, including multiple burr holes, EDAS, and STA-MCA, before enrollment;

5) No clear surgical indication, or the patient refuses surgical treatment for personal reasons and requests conservative treatment;

6) Signed informed consent form.

5.3 Exclusion Criteria

1) Previous history of any form of intracranial hemorrhage, such as subarachnoid hemorrhage, intracerebral hemorrhage, or intraventricular hemorrhage; history of symptomatic ischemic stroke; frequent TIA attacks before enrollment, defined as 3 or more attacks within 7 days; or history of epileptic seizures;

2) Concomitant cerebrovascular diseases that may significantly affect perioperative risk or outcome assessment, such as intracranial aneurysm, cerebral arteriovenous malformation, or arteriovenous fistula requiring concurrent treatment;

3) Previous history of severe craniocerebral trauma, brain tumor, encephalitis, meningitis or other central nervous system inflammation, other major craniocerebral disease, any form of invasive brain treatment, or radiotherapy;

4) Planned cerebral revascularization surgery within 3 months;

5) Severe cardiac dysfunction (ejection fraction $<$ 50% or NYHA class III-IV heart function), hepatic dysfunction (ALT or AST $>$ 2 times the upper limit of normal), or renal insufficiency (serum creatinine $>$ 3 mg/dL); concomitant major systemic disease, such as a history of unstable angina, acute coronary syndrome, asthma, or chronic obstructive pulmonary disease (COPD); severe non-cardiovascular comorbidity with expected survival $<$ 1 year; or other severe comorbidity that the investigator judges would significantly increase study risk;

6) Contraindication to aspirin:

a. Known allergy;

b. Severe renal insufficiency (creatinine $>$ 1.5 times the upper limit of normal) or severe hepatic insufficiency (ALT or AST $>$ 2 times the upper limit of normal);

c. Severe heart failure (NYHA class III-IV);

d. Coagulation disorder or history of systemic bleeding;

e. History of thrombocytopenia or neutropenia;

f. History of drug-induced hematological disease or liver function injury;

g. White blood cell count $<$ 2 x 10^9/L or platelet count $<$ 100 x 10^9/L;

h. History of gastrointestinal bleeding within 3 months before enrollment, or definite history of gastric ulcer or gastritis;

i. Other contraindications to aspirin.

7) Contraindication to ischemic conditioning:

a. Concomitant peripheral vascular disease of the upper or lower limbs, especially significant stenosis or occlusion of the brachial artery or the ulnar or radial artery, or a condition judged by the investigator to be unsuitable for upper-arm cuff compression to implement remote ischemic treatment;

b. Conditions that may affect the safety of upper-limb remote ischemic conditioning (RIC), including but not limited to severe skin or soft-tissue infection/damage, obvious lymphedema, arteriovenous fistula or dialysis fistula, recent deep venous thrombosis, or investigator judgment that the patient cannot tolerate upper-arm cuff compression, such as severe pain or repeated subcutaneous bleeding;

c. Known history of allergy to the RIC device or its component materials;

8) Need for aspirin and/or antiplatelet drugs because of diseases other than moyamoya disease, such as systemic disease, circulatory disease, or hematological disease; or continuous use of other antiplatelet drugs for >= 5 days before enrollment with the last dose <= 10 days before enrollment;

9) Need for anticoagulant therapy, including conditions requiring anticoagulation such as atrial fibrillation, artificial heart valve, known or suspected endocarditis, or venous thrombosis; or use of heparin or oral anticoagulants within 10 days before enrollment;

10) Pregnant women, suspected pregnancy (women of childbearing potential without effective contraception and with a positive pregnancy test), or lactating women;

11) Conditions affecting completion of key follow-up assessments, such as severe cognitive impairment or psychiatric disorder causing inability to cooperate with assessment, or a clear expectation that follow-up cannot be completed;

12) Current participation in another interventional clinical trial, where the investigator considers that such participation may interfere with outcome assessment in this study.

VI. Intervention Regimens

After randomization, all patients will be divided into four groups: control group (aspirin placebo + sham ischemic conditioning procedure); intervention group 1 (aspirin treatment + sham ischemic conditioning procedure); intervention group 2 (aspirin placebo + ischemic conditioning); and intervention group 3 (aspirin treatment + ischemic conditioning). All patients will begin pharmacological intervention and ischemic conditioning intervention within 24 hours after randomization is completed.

6.1 Pharmacological Intervention

Aspirin or placebo will be taken orally every morning for 1 year. To ensure medication adherence, study drugs will be dispensed and regularly recovered for pill counting.

Aspirin: 100 mg, orally on an empty stomach in the morning, once daily;

Placebo: consistent with aspirin in dosage form, dose, packaging, and appearance; 100 mg, orally on an empty stomach in the morning, once daily.

6.2 Ischemic Conditioning Intervention

The first 3 months after randomization will be the intensive phase, during which ischemic conditioning or sham procedure treatment will be completed once daily. Months 4 to 6 after randomization will be the maintenance phase, during which ischemic conditioning or sham procedure treatment will be completed no fewer than 4 times per week, with a maximum of once per day.

Real ischemic conditioning procedure group: the ischemic conditioning device will be used once daily, including 5 treatment cycles. After blood pressure is measured in both arms, the upper limit of the bilaterally measured blood pressure will be used as the inflation value. The cuffs on both upper limbs will be inflated and maintained for 5 minutes, followed by deflation for 5 minutes. Each treatment session will last 45

minutes.

Sham ischemic conditioning procedure group: the sham ischemic conditioning device will be used once daily, including 5 treatment cycles. The cuffs on both upper limbs will be inflated to 60 mmHg and maintained for 5 minutes, followed by deflation for 5 minutes. Each treatment session will last 45 minutes.

6.3 Intervention Discontinuation

If a patient experiences a safety endpoint event, an adverse reaction related to ASA, or an adverse reaction related to RIC, medication may be suspended or discontinued, and management will be provided according to the emergency treatment plan.

VII. Study Implementation

7.1 Preparatory Work

1) Preparation: In this study, each study center will use an electronic data capture (EDC) system via the Internet to process patient enrollment and data collection.

2) Hospital registration

The person in charge of the study office will send the list of hospitals and principal investigators to the data center. Each study subcenter will enroll competitively under the principle of total enrollment control until the planned sample size is reached.

3) EDC system user registration

The principal investigators of each hospital will send the names and emergency contact information of EDC system users, consisting of assistant investigators at each hospital, to the data center through the study office. If there are no problems or questions, the data center will provide IDs and passwords.

7.2 Enrollment

1) Preliminary screening

After patients are diagnosed with moyamoya disease in the outpatient clinic, they will undergo preliminary screening. The principal investigator or assistant investigator will screen patients suitable for this study according to "V. Subject Selection."

2) Obtaining informed consent

The study content and relevant benefits and risks will be explained to the patient or the patient's legal representative, and the informed consent form will be signed.

3) Confirmation of eligibility and data entry

The principal investigator or assistant investigator will complete the patient baseline

data form according to "5.2 Inclusion Criteria and 5.3 Exclusion Criteria" and confirm eligibility. The investigator will log in to the patient enrollment website and enter and transmit the necessary information. The EDC system will receive the necessary information, confirm the details, and display eligibility or ineligibility on the website. According to the study progress of each center, the number of enrolled cases may be adjusted, but confirmation from the data management center is required.

4) Confirmation of the patient enrollment contact form (completion of enrollment)

The principal investigator or assistant investigator will confirm the details. If eligibility information is displayed, the enrollment date and study ID assigned by the EDC system shall be entered in the "Subject Enrollment List." At this point, the patient will be considered enrolled as a subject in this study. Study treatment may begin only after patient enrollment is completed by the principal investigator or assistant investigator.

7.3 Randomization

7.3.1 Method

A central randomization system will be used, and all enrolled patients will be randomized in a 1:1:1:1 ratio to four groups: control group, aspirin placebo + sham ischemic conditioning procedure; intervention group 1, aspirin treatment + sham ischemic conditioning procedure; intervention group 2, aspirin placebo + ischemic conditioning; and intervention group 3, aspirin treatment + ischemic conditioning. After informed consent is obtained, all enrolled patients will be randomized using the online randomization system with center-stratified randomization. The randomization process will be fully recorded to ensure allocation concealment and traceability of subsequent data. In emergencies, authorized personnel may apply for unblinding through the central randomization system, and the process and reason for unblinding will be recorded in detail.

7.3.2 Randomization factor

Study center.

7.3.3 Acquisition of randomization results

After enrollment, the principal investigator or subinvestigator will obtain the randomization results for study treatment from the EDC system, including the drug number and device number. The randomization results will be controlled and retained by the lead center.

7.3.4 Notes

1) If the entered information is incomplete, patient enrollment will not be accepted until all required information has been entered.

2) Except in cases of refusal to use data, once a patient is enrolled, the patient will not be removed from the study database. If duplicate enrollment occurs, the first enrollment information, namely the patient enrollment number, shall prevail.

3) If an error or duplicate enrollment is found, contact the lead center.

7.4 Blinding Design and Unblinding Procedures

7.4.1 Description of blinding

1) Double blinding: randomization will be performed through the central randomization system. The system will automatically generate the allocation results according to a preset block length, with randomly varying block length to enhance allocation concealment, and will provide investigators only with the corresponding drug number and device number. Investigators and subjects will remain blinded to the specific group assignment throughout the study.

2) Blinded endpoint assessment: endpoint events will be assessed by trained third-party personnel through standardized telephone interviews conducted without knowledge of patient randomization or actual treatment status. All follow-up telephone calls will be recorded and follow-up reports will be generated.

7.4.2 Emergency unblinding procedure

If an adverse event (AE) occurs, unblinding may be performed only under special circumstances, namely when knowledge of the drug composition is essential for patient treatment. If possible, the investigator should contact the monitoring team before unblinding. If an investigator at a study subcenter considers unblinding necessary, he or she must immediately notify the person in charge of that subcenter and, after obtaining the subcenter head's agreement, notify the monitor and sponsor as soon as possible. All telephone calls will be recorded by the CRO. If unblinding occurs, the investigator shall record in writing the date, time, and reason for unblinding, and the study drug or RIC will be discontinued.

7.5 Management of Study Drug and Ischemic Conditioning Devices

7.5.1 Drug and device dispensing

After enrollment, the drug management personnel will dispense 3 boxes of aspirin or placebo according to the patient's group assignment, covering study medication from day 1 to month 3 +/- 7 days. Thereafter, every 3 months the patient will bring or mail back the drug boxes at the visit and exchange them for study medication for the next study phase (3 months).

Device management personnel will dispense the pre-programmed standard ischemic conditioning device or sham ischemic conditioning device according to the patient's group assignment, and will train the subject in standardized use of the ischemic conditioning device.

7.5.2 Responsibilities for drug and device management

Investigators, pharmacists, or other personnel who store and distribute drugs shall ensure that study drugs used in the clinical trial are safely stored and used according to the sponsor's requirements and in compliance with current rules and regulations. All study drugs will be distributed according to the study protocol, and the investigator is responsible for ensuring accurate records of distribution and return of study drugs. Any

quality problems identified during receipt or use of study drugs, such as defects in appearance, labeling, or expiration date, shall be reported to the sponsor in a timely manner.

7.5.3 Recovery and destruction of study drugs

The investigator or pharmacist shall establish detailed records for recovered study drugs, and the investigator and monitoring team shall jointly confirm these records. The investigator shall not destroy unused or partially used study drugs unless written authorization is provided by the principal investigator. If a quality defect exists in the study drug, the investigator will implement recall and recovery procedures. In this situation, the investigator is responsible for meeting any requirements raised by the principal investigator to recall the study drug and eliminate potential harm.

7.5.4 Intervention quality control:

① At each follow-up visit, the subject will return remaining drug boxes, and the investigator will count the remaining tablets. The actual number of tablets taken will be recorded, and aspirin adherence will be assessed using the adherence rate (adherence rate = actual number of tablets taken / required number of tablets x 100%). An adherence rate lower than 80% or higher than 120% will be considered poor adherence;

② The ischemic conditioning device has a built-in recording chip that can be exported and checked at each follow-up visit. During the intensive phase, fewer than 4 interventions per week will be recorded as 1 protocol violation; during the maintenance phase, fewer than 3 interventions per week will be recorded as 1 protocol violation. More than 1 intervention per day will be recorded as 1 protocol violation, and 3 consecutive violations will be considered poor adherence;

③ A treatment log will be issued. Medication use and ischemic conditioning use will be recorded daily and cross-checked against tablet counts and the built-in counting chip of the ischemic conditioning device;

④ Investigators will remind patients by telephone or text message each month

to continue medication. For non-volitional decreases in adherence caused by memory decline, family members will be asked to assist. Quality control personnel will conduct monthly checks to ensure completion of the intervention.

7.6 Concomitant Medication and Treatment

During the study, any drug treatment, surgery, vascular interventional treatment performed after enrollment, and any change in medication during the study shall be recorded in the case report form.

7.6.1 Prohibited concomitant medications

1) Antiplatelet drugs other than aspirin: clopidogrel, ticagrelor, dipyridamole, cilostazol, ticlopidine, prasugrel, GPIIb/IIIa receptor antagonists, ozagrel, etc.

2) All anticoagulants.

3) Thrombolytic drugs: rt-PA, urokinase, streptokinase, etc. Patients who received intravenous or intra-arterial thrombolytic therapy within 24 hours before enrollment shall be excluded. If a patient receives intravenous or intra-arterial thrombolytic therapy after enrollment, study treatment must be suspended for more than 24 hours and may then be resumed.

4) Batroxobin, defibrase, snake venom preparations, lumbrokinase, etc.

5) Nonsteroidal anti-inflammatory drugs (Cox-1 and Cox-2 inhibitors). Long-term use, defined as more than 7 days after enrollment, of nonsteroidal anti-inflammatory drugs other than aspirin (Cox-1 and Cox-2 inhibitors) is a protocol violation. If absolutely necessary, nonsteroidal anti-inflammatory drugs should be started 24 hours after suspending the study drug.

6) P-glycoprotein substrate: digoxin. If digoxin is absolutely required, the digoxin dose should be reduced as appropriate, and blood digoxin concentration should be closely monitored.

7.6.2 Permitted concomitant medications

Medications other than those listed above are permitted concomitant medications. Patients with underlying diseases, such as hypertension, diabetes, coronary heart disease, and epilepsy, may use diuretics, beta-blockers, ACEIs, ARBs, calcium channel blockers, lipid-lowering drugs, coronary vasodilators, antidiabetic drugs including insulin, antiepileptic drugs, etc. Disease diagnosis, drug name, dose, and administration method must be recorded in detail in the case report form. If other treatments must be added because of special circumstances, such as another disease occurring during the study, this must be explained in the case report form, including disease diagnosis, drug, dose, and administration method.

1) In emergencies, such as acute coronary syndrome or the need for percutaneous coronary intervention (PCI) requiring intensified antiplatelet therapy, the antiplatelet drug dose may be increased temporarily. After the condition stabilizes, the study dose shall be resumed, and medication adjustments shall be recorded in detail in the CRF.

2) H2 receptor blockers: all may be used except cimetidine.

3) Proton pump inhibitors (PPIs): if clinically needed, rabeprazole is recommended. PPIs other than omeprazole and esomeprazole, such as dexlansoprazole, lansoprazole, and pantoprazole, may be used.

4) Statins: the dose of simvastatin or lovastatin used in combination should not exceed 40 mg/day.

5) Drugs that may induce bradycardia: heart rate should be monitored when drugs such as beta-blockers and calcium channel blockers are used together with ticagrelor.

6) Selective serotonin reuptake inhibitors (SSRIs): paroxetine, sertraline, and citalopram may increase bleeding risk. If concomitant use is necessary, caution is required and bleeding events should be closely monitored.

7.5.3 Surgery and invasive procedures

If surgery or an invasive procedure is absolutely required within 3 months after enrollment: for surgery with the possibility of major bleeding, the study drug should be

discontinued at least 5 days before surgery and restarted after surgery when the investigator considers the bleeding risk to be low; for other surgeries or invasive procedures, the study drug may be continued or suspended according to the investigator's judgment. If infusion therapy is needed, ischemic conditioning may be stopped from the day of infusion and restarted within one week after infusion can be discontinued.

7.7 Management of Temporary Discontinuation, Permanent Discontinuation, or Loss to Follow-up

The study drug should be used continuously whenever possible. If the study drug is discontinued, it should be determined whether temporary discontinuation is possible; permanent discontinuation is the last option. Any discontinuation shall be completely recorded on the corresponding page of the CRF. Under all circumstances, patients should remain in the trial for as long as possible. Discontinuation of the study drug does not mean discontinuation of follow-up or withdrawal from the study; study assessments and follow-up should continue.

7.7.1 Temporary Discontinuation of Study Drug

If the study drug must be temporarily discontinued, it should be restarted as soon as possible. The study drug should be temporarily discontinued in the following situations:

1) Severe thrombocytopenia (platelet count < 50,000/uL, i.e., 50 x 10^9/L). After severe thrombocytopenia resolves, the patient may restart the study drug;

2) Severe bleeding, as defined by GUSTO;

3) Need to use prohibited concomitant medications, see Section 7.6;

4) Surgery or procedure that may cause major bleeding, see Section 7.6. For other surgeries or invasive procedures, the study drug may be continued or temporarily

discontinued according to the investigator's judgment.

Once the investigator determines that the study drug is unlikely to be related to the event and that there are no other contraindications to continuing the study, the study drug should be restarted. Restarting the study drug should be performed under close and reasonable monitoring. At the same time, all periods of temporary study-drug discontinuation shall be recorded on the corresponding page of the CRF.

7.7.2 Permanent Discontinuation of Study Drug or RIC Treatment

1) Patient decision: the patient may discontinue treatment at any time, provided that further treatment is not affected.

2) Investigator decision, including but not limited to the following situations:

① Pregnancy or discontinuation of medication because of preparation for pregnancy;

② Erroneous enrollment that does not meet the inclusion/exclusion criteria and would place the patient at higher risk;

③ Serious noncompliance with the study protocol;

④ An adverse event that the investigator believes would place the patient at higher risk if treatment were continued;

⑤ Definite need for anticoagulant therapy;

⑥ After temporary discontinuation of the drug or RIC treatment, the investigator judges that the patient is unsuitable for resuming the study treatment;

7.6.3 Management Plan for Patients Who Permanently Discontinue Medication

Patients who permanently discontinue the study drug shall receive routine treatment. The investigator shall ask in detail about the reason for study-drug discontinuation and whether adverse events occurred, follow up adverse events, and record them in the corresponding location in the CRF. The investigator will recover all unused study drugs. All patients who stop using the study drug before the final follow-

up shall complete the scheduled follow-up or be followed until they recover from the adverse event or their condition becomes stable, whichever period is longer. The investigator shall record all confirmed premature withdrawals on the corresponding page of the CRF.

7.6.4 Loss to Follow-up

The investigator shall make every effort to contact each patient, determine the reason for loss to follow-up, and assess the patient's health status. The CRF for a patient lost to follow-up shall be completed up to the last follow-up.

7.7 Withdrawal from the Study

Patients who have withdrawn from the study cannot re-enter the study. The patient's enrollment number and treatment drug cannot continue to be used. The investigator shall contact the monitoring team to jointly confirm treatment interruption and/or patient withdrawal.

Criteria for withdrawal from the study:

1) Participation in another interventional clinical trial before completion of this study, where the investigator considers that it may interfere with outcome assessment in this study; 2) loss to follow-up: after reasonable follow-up efforts, the subject still cannot be contacted, or the subject clearly refuses further follow-up, resulting in inability to obtain key clinical outcome information within the prespecified time window, including the primary outcome and key long-term clinical outcomes; 3) during follow-up, the subject is found to have seriously violated the study protocol for any reason; 4) the subject or the subject's legal representative withdraws informed consent and clearly requests withdrawal from the study, including refusal of further follow-up; 5) a serious adverse event occurs and the investigator judges that continued participation in the study or continued RIC intervention may increase the subject's risk; 6) unblinding occurs for any reason during the study; 7) a female subject becomes

pregnant during follow-up, requiring termination of study intervention; the potential effects of previous study intervention on the subject shall be assessed by obstetrics and gynecology specialists, and the subject shall be excluded from the study and followed until the end of pregnancy.

Note: If the subject stops RIC intervention but agrees to continue follow-up and outcome assessment, this will not be considered withdrawal from the study. Follow-up should be completed as far as possible, and the subject should be included in the primary analysis according to the intention-to-treat (ITT) principle.

VIII. Data Collection

Investigators shall enter data into the CRF in a timely manner according to the study protocol and completion manual, and shall ensure accurate, complete, and timely recording of data and responses to data queries in accordance with the clinical study protocol. Imaging data from all patients will be collected in DICOM format, and complete information for each MRI sequence (T1 + T2 + DWI + FLAIR + MRA) will be retained. Follow-up telephone calls will be stored as audio recordings.

IX. Known and Potential Risks and Benefits of the Project, and Risk Management Plan

10.1 Potential Benefits

For subjects, aspirin may reduce the risk of microembolus formation by inhibiting platelet aggregation, while ischemic conditioning may improve cerebral blood flow reserve by activating endogenous protective mechanisms and thereby delay disease progression. Combined treatment may produce a synergistic effect. All subjects will receive standardized medical follow-up and imaging monitoring during the study.

10.2 Potential Risks

The interventions involved in this study include aspirin and ischemic conditioning therapy, as follows:

1) Side effects of aspirin: increased bleeding tendency, including intracranial hemorrhage, hematoma, epistaxis, genitourinary bleeding, gingival bleeding, anemia, hemolysis, hematuria, dyspepsia, gastrointestinal and abdominal pain, gastrointestinal ulcer and bleeding; kidney injury and acute renal failure; transient elevation of transaminases; drug allergy; asthma; urticaria; angioneurotic edema; or shock.

2) Side effects of ischemic conditioning therapy: local adverse reactions of the limbs, such as skin indentation, ecchymosis, blisters, limb numbness or discomfort, or necrosis caused by cuff compression; and limb deep venous thrombosis.

Combined treatment may bring additive risks, but the risk spectra of the two interventions do not overlap.

10.3 Definition of Adverse Events

1) Adverse event (AE):

An AE refers to any unfavorable medical event that occurs after a subject receives

the study drug and device. It may manifest as symptoms, signs, disease, or abnormal laboratory findings, but it does not necessarily have a causal relationship with the investigational product. AEs include serious AEs (SAEs) and nonserious AEs.

Research personnel shall record in detail any adverse event experienced by the subject, including: description of the adverse event and all related symptoms, time of occurrence, severity, relationship to the study drug and device, duration, measures taken, final outcome, and prognosis.

Note: Adverse events occur after administration of the study drug and device; however, for the purpose of collecting "safety information" in the clinical trial, any unfavorable medical event occurring after informed consent is signed shall be collected and recorded. After informed consent is signed and before medication administration, unfavorable medical events shall be recorded in the eCRF as medical history/concomitant disease rather than as AEs, unless they are injuries/damage caused by clinical laboratory procedures, in which case they shall be recorded as AEs.

2) Serious adverse event (SAE)

An SAE refers to an adverse event that occurs after the subject receives the study drug and uses the ischemic conditioning device and that meets one or more of the following criteria:

- Death;
- Life-threatening. Note: the definition of life-threatening severity means that the event placed the patient at immediate risk of death at the time of occurrence, not that the event would have caused death if it had been more severe;
- Permanent or severe disability or loss of function;
- Requires hospitalization or prolongs hospitalization;
- Congenital anomaly or birth defect;

- Important medical event that may endanger the subject or require medical intervention to prevent the above outcomes.

Special circumstances: In clinical studies, AEs that lead to hospitalization or prolonged hospitalization should be considered SAEs, excluding admissions in the following circumstances: rehabilitation facility; nursing home; routine emergency room admission; same-day surgery, such as outpatient, same-day, or ambulatory surgery. Hospitalization or prolonged hospitalization unrelated to worsening of an AE is also excluded. Examples include admission for a pre-existing disease without occurrence of a new AE or worsening of the pre-existing disease, such as evaluation of a laboratory abnormality that existed before the study and has continued; hospitalization for administrative reasons, such as annual routine physical examination; elective hospitalization unrelated to worsening of an AE, such as elective cosmetic surgery; preplanned treatment or surgery, which should be recorded in baseline data; admission solely for use of blood products; and hospitalization for administrative or social welfare reimbursement reasons, such as hospitalization for convalescence or hospitalization because of medical insurance reimbursement. Such situations shall not be reported as SAEs.

Diagnostic or therapeutic invasive procedures, such as surgery, and noninvasive procedures should not be reported as SAEs. However, if the disease condition leading to such a procedure meets the definition of an AE, it shall be reported. For example, acute appendicitis occurring during the AE reporting period shall be reported as an AE, while the appendectomy performed for it shall be recorded as the treatment method for that AE.

3) Adverse drug reaction (ADR)

An adverse drug reaction refers to any harmful or unintended human response in a clinical trial that may be related to the investigational product. There is at least a reasonable possibility of a causal relationship between the investigational product and the adverse event, meaning that relatedness cannot be excluded.

4) Suspected unexpected serious adverse reaction (SUSAR)

A suspected unexpected serious adverse reaction refers to a suspected and unexpected serious adverse reaction whose nature and severity in clinical presentation exceed the existing information in the investigator's brochure for the investigational drug, the package insert of an approved drug, or the summary of product characteristics.

10.4 Recording of Adverse Events

AEs will be monitored throughout the study. Investigators are responsible for recording all AEs observed during the study and information on discontinuation caused by DAE, namely discontinuation of study drug because of adverse events. The following items shall be included:

(1) Name of adverse event: describe the AE using medical terminology rather than the subject's original wording. Where applicable, symptoms, signs, abnormal laboratory tests, and diagnoses should be included, with priority given to the medical diagnosis. If an abnormal laboratory test is part of a syndrome, record the syndrome or diagnosis, such as anemia, rather than the laboratory test result, such as decreased hemoglobin. If the same AE occurs more than once in the same subject and the subject recovered between the two events, the two AEs should be recorded separately.

(2) Start date/time of the adverse event: the time when the subject first experiences the AE or AE-related symptoms. If the AE is a clinically significant abnormal laboratory test or examination result, the occurrence date is the sampling date.

(3) End date/time of the adverse event: the date when the AE or AE-related symptoms end. If the AE is still ongoing, the end date does not need to be completed.

(4) Causal relationship between the adverse event and the study drug.

(5) Severity of the adverse event will be assessed and graded according to NCI-CTCAE 5.0, from grade 1 to grade 5.

(6) Whether it is an SAE (yes/no).

(7) Measures taken for the adverse event:

a) No measures taken;

b) Measures taken for the study drug and device: regimen unchanged, permanently discontinued, or not applicable;

c) Medication treatment, with concomitant medication recorded;

d) Non-drug treatment, with the treatment method and details recorded;

e) Other.

(8) Outcome of the adverse event, including:

a) Recovered/resolved: the "end date of the serious/adverse event" shall be specified.

b) Recovering/resolving: the event has not fully resolved, but the subject is in the recovery phase and requires follow-up.

c) Not recovered/not resolved: the event is ongoing.

d) Recovered/resolved with sequelae: only when the subject will have long-term or lifelong sequelae, such as blindness caused by diabetes or hemiplegia after stroke. The "end date of the serious/adverse event" shall be specified.

e) Death: the "end date of the serious/adverse event" shall be specified. When the adverse event is fatal, the time of death shall be recorded.

f) Unknown: the investigator cannot obtain information on the adverse event, for example because the subject is lost to follow-up or refuses reexamination.

If the adverse event outcome is assessed as "recovering/resolving," "not recovered/not resolved," or "unknown," the adverse event end date may be temporarily omitted.

If the adverse event outcome is assessed as "recovered/resolved," "recovered/resolved with sequelae," or "death," the adverse event end date must be recorded. It must also be recorded whether the subject withdrew from the study because of this adverse event.

10.5 Assessment of the Relationship Between Adverse Events and the Investigational Treatment:

Investigators will determine the causal relationship between AEs and the study drug and device according to the following criteria, and may also refer to the table below:

① Definite Related: There is a reasonable temporal sequence between occurrence of the AE and use of the study drug and device. The AE is a known adverse reaction of the study drug and device. The AE improves or disappears after discontinuation, recurs after rechallenge, and cannot be explained by the subject's underlying disease.

② Probably Related: There is a reasonable temporal sequence between occurrence of the AE and use of the study drug and device. The AE is a known adverse reaction of the study drug and device. The reaction improves or disappears after discontinuation of the study drug and device and cannot be explained by the subject's underlying disease. The effect of rechallenge is unknown or rechallenge cannot be performed.

③ Possibly Related: There is a reasonable temporal sequence between occurrence of the AE and use of the study drug and device. The AE is a known or suspected adverse reaction of the study drug and device, but other factors may have caused the event, such as disease or concomitant medication. The effect after discontinuation is unclear, ambiguous, or lacks decisive information.

④ Unlikely to be Related: There is a reasonable temporal sequence between occurrence of the AE and use of the study drug and device, but the event is not a known type of drug adverse reaction and is highly likely to have been caused by the subject's disease or other treatment.

⑤ Not Related: There is no reasonable temporal sequence between occurrence of the AE and use of the study drug and device, for example the event occurred before use of the investigational drug; the event is not a known drug adverse reaction; or the AE is

clearly caused by other factors such as the subject's disease, other treatment, or concomitant medication.

⑥ Unable to judge.

The above items ① to ③ shall be recorded as adverse drug reactions. Incidence of adverse reactions = (number of cases in ① + ② + ③) / number of cases in the safety dataset x 100%.

10.6 Serious Adverse Event Reporting

For serious adverse events, investigators must immediately take corresponding management measures: complete the Serious Adverse Event Report Form; immediately notify the corresponding responsible person of the sponsor; send the signed and dated relevant pages of the case report form to the corresponding responsible person of the sponsor, together with copies of all examinations and the dates on which these examinations were completed. Patient privacy must be protected, and patient identifying information must be removed from copies of clinical source documents provided to the sponsor. Laboratory results should include normal reference ranges.

Any serious adverse event shall be reported within 48 hours after occurrence. The serious adverse event shall be entered in the corresponding location in the CRF, signed, and preferably reported to the safety committee in writing, by fax, or by email. The cause of the serious adverse event and the measures taken shall also be recorded.

10.7 Risk Management

High-risk patients will be excluded through strict screening before enrollment. During the study, adverse events will be monitored through regular follow-up, and patients will receive education on risk signals. If an adverse event occurs, measures such as suspension or termination of the intervention, clinical treatment, and emergency unblinding will be taken according to severity, and the event will be reported to the ethics committee as required. Ischemic conditioning will be performed by trained and

qualified research personnel. Pressure will be individually adjusted according to patient tolerance, and local injuries will be treated promptly.

All recording and reporting of safety information will strictly comply with the relevant provisions of the National Medical Products Administration Good Clinical Practice for Drug Clinical Trials and Good Clinical Practice for Medical Device Clinical Trials. All adverse events occurring during the study, regardless of whether they are related to the interventions, must be recorded in detail in the case report form, including the name of the adverse event, time of occurrence, severity, duration, management measures taken, relationship judgment with aspirin or the ischemic conditioning device, and outcome. Serious adverse events shall be reported through the central randomization system within 48 hours after awareness, and written notification shall be sent simultaneously to the project leader or project contact person and the ethics committee; they shall also be reported to the competent health authority within the required time limit. All adverse events must be followed until resolution. For serious adverse events that lead to study termination, subjects must receive long-term follow-up until the outcome is clear, and a formal follow-up report must be submitted. After study completion, all safety data will be summarized and analyzed and fully presented in the final study report to ensure the scientific integrity of the study and the protection of subjects' rights and interests.

Overall, the risks of this study are controllable, and the potential benefits outweigh the foreseeable risks.

10.8 Adverse Event Management Process

(1) Research personnel shall obtain information on all adverse events and attempt to establish a diagnostic standard for adverse events based on the patient's symptoms, signs, and/or clinical information, rather than recording individual symptoms or signs only;

(2) After becoming aware of an adverse event, the investigator shall provide active medical management. If protocol deviation is necessary for management, it shall be recorded as a protocol deviation, and whether the subject should continue follow-up or withdraw from the study shall be determined according to the severity of the deviation and the subject's condition;

(3) All adverse events shall be recorded in the source medical record and in the case report form;

(4) The investigator shall determine the outcome of the adverse event and judge whether it is a serious adverse event. If it is a serious adverse event, the investigator must immediately provide proper management or rescue treatment to protect the subject's safety;

(5) The cause of the adverse event shall be assessed and documented in the case report form;

(6) All adverse events must be assessed by the investigator, managed as necessary and in a timely manner, including temporary observation, and followed until resolution, stabilization, another explanation for the adverse event, or loss to follow-up of the subject;

(7) Once the problem is resolved, the adverse event record in the case report form shall be updated promptly;

(8) The investigator may arrange additional examinations during follow-up to identify the cause of the adverse event.

(9) All SAEs shall be followed until they are fully resolved or the outcome will no longer change, and at least one follow-up or summary report shall be provided. The report shall describe in detail the management given to the subject since the occurrence of the SAE, the course and outcome of the condition, the final diagnosis, and the judgment of relationship with the investigational drug. After the SAE summary report is completed, the investigator shall send it to the sponsor.

10.9 Management of Serious Adverse Events

(1) Once the investigator identifies a serious adverse event, appropriate medical treatment measures shall be provided immediately and on site in a timely manner to fully protect the subject's health and life safety;

(2) The investigator shall clearly determine the relationship between the serious adverse event and the investigational drug. If the serious adverse event is judged not to be related to the investigational drug, symptomatic treatment shall be provided, and whether the subject withdraws will be decided by the investigator. If the investigator determines that the serious adverse event is related to the investigational drug, the subject shall immediately be withdrawn from the clinical trial and receive symptomatic management and subsequent treatment;

(3) The investigator shall follow regulatory requirements and report step by step according to the pre-established reporting procedures;

(4) The investigator shall follow up the serious adverse event and complete the initial report, follow-up report, and summary report for the serious adverse event;

(5) The investigator shall conduct follow-up monitoring for subjects who experience serious adverse events to fully protect their rights and interests.

10.10 Contents of Serious Adverse Event Reports

The investigator shall complete the Serious Adverse Event Report Form. The report shall include the following sections, including but not limited to:

1) SAE initial report information: main description of the event; general information of the subject; investigator's judgment on the cause of the event.

2) SAE supplementary report information: detailed description of the event, including copies of hospital medical records, autopsy report, and other useful documents required; assessment of the event and analysis of the causes, including concomitant medication and concomitant diseases. For death cases, if an autopsy report

is available, it shall be reported immediately.

3) The investigator shall notify other investigators participating in the clinical trial of this SAE.

When completing the Serious Adverse Event Report Form, the investigator shall describe in detail the course of occurrence, diagnosis, treatment provided, possible relationship with the drug and the basis for that judgment, and final outcome of the adverse event. If the diagnosis is temporarily unclear, if the diagnosis is changed after reporting, or if the subject's condition changes significantly, such as progression from prolonged hospitalization to death, a follow-up report shall be completed and reported according to the initial reporting procedure.

10.11 Pregnancy Reporting

During the study, if a female subject using the study drug or the partner of a male subject becomes pregnant, the investigator shall complete a pregnancy report form within 72 hours after becoming aware of the pregnancy and submit it to the ethics committee and sponsor. Any female subject who becomes pregnant, intrauterine pregnancy, during participation in this study must withdraw from the study and immediately discontinue the study drug.

Female subjects or partners of male subjects who experience a pregnancy event must be followed until the infant is delivered at term to determine the pregnancy outcome, including early termination of pregnancy, and maternal and infant status. Pregnancy complications and elective termination of pregnancy for medical reasons must be reported as AEs or SAEs. Spontaneous abortion, stillbirth, and congenital developmental abnormalities must be reported as SAEs.

10.12 Reporting of Suspected Unexpected Serious Adverse Reactions

After receiving safety-related information from any source, the investigator shall immediately analyze and assess the information, including seriousness, relationship

with the investigational drug, and whether the event is expected. The investigator shall rapidly report suspected unexpected serious adverse reactions to all investigators participating in the clinical trial, clinical trial institutions, and ethics committees:

(1) For fatal or life-threatening unexpected

serious adverse reactions, reporting shall be made as soon as possible after first awareness, but no later than 7 days, and follow-up information shall be reported and completed within the subsequent 8 days.

(2) For unexpected serious adverse reactions that are not fatal or life-threatening, reporting shall be made as soon as possible after first awareness, but no later than 15 days.

Note: The day when the investigator first becomes aware is day 0.

Serious adverse events occurring after completion of the clinical trial or completion of follow-up shall also be rapidly reported by the investigator if they are unexpected serious adverse reactions.

After the initial report, serious adverse reactions shall continue to be tracked, and new information or changes to previous reports shall be submitted in a timely manner as follow-up reports. The reporting deadline is within 15 days after obtaining new information.

XI. Ethical Considerations

Before the study begins, the clinical study may be implemented only after the trial protocol has been approved by the ethics committee. Before each subject is enrolled in this study, the investigator is responsible for fully explaining to the subject or the subject's legal representative the purpose, procedures, and possible risks of this study, as well as information on alternative treatments, and for obtaining written informed consent. Subjects should be informed that they have the right to withdraw from the study at any time. The informed consent form shall be retained as a clinical study document for future reference. During the study, subjects' personal information will be protected from disclosure, and patient data will be kept confidential. Publications and academic communications will not involve personal patient information, thereby protecting patient privacy.

XII. Statistical Analysis

12.1 Statistical Methods for Baseline Data Analysis

Descriptive statistics: continuous variables, such as age and blood pressure, will be expressed as mean +/- standard deviation or median (interquartile range), and categorical variables, such as sex and comorbidities, will be expressed as frequencies and percentages.

Between-group balance testing: analysis of variance or the Kruskal-Wallis test will be used for continuous variables, and the chi-square test or Fisher's exact test will be used for categorical variables, to assess whether baseline characteristics are comparable across groups after randomization.

12.2 Statistical Methods for Endpoint Events

Survival analysis: the Kaplan-Meier method will be used to estimate event rates in each group and plot survival curves. Between-group comparisons will be performed using the Log-rank test.

Multivariable analysis: a Cox proportional hazards model will be used, with treatment group as the independent variable and with adjustment for center as a stratification factor and other baseline covariates that may affect prognosis, such as age, sex, and risk factors. Hazard ratios (HRs) and 95% confidence intervals will be calculated.

Logistic regression model: for binary variables, center and baseline covariates will be adjusted for, and odds ratios (ORs) and 95% CIs will be calculated. For ordinal categories, such as changes in Fazekas score, ordinal logistic regression or nonparametric tests may be used. For continuous variables, such as volume change, analysis of covariance (ANCOVA) or mixed linear models may be used.

Multiple comparisons: pairwise comparisons among the four groups, such as

intervention group 1 vs control group, intervention group 2 vs control group, intervention group 3 vs control group, and comparisons among intervention groups, will be performed while controlling type I error. Bonferroni correction or Dunnett's test, using the control group as reference, may be used.

Intention-to-treat analysis (ITT): the primary analysis will be based on the ITT principle, meaning that all randomized patients will be included in the analysis. Missing data will be handled using appropriate methods, such as multiple imputation or last observation carried forward.

Per-protocol analysis set (PP): as a sensitivity analysis, only patients who complete follow-up and have good adherence will be included.

XIII. Submission and Retention of Study Materials

All materials for this study will be retained strictly in accordance with the Good Clinical Practice and the archive management requirements of medical institutions. A separate file cabinet will be established to store core documents, including the study protocol, investigator's brochure, ethics approvals, and agreements entrusted to each center. Original medical records, informed consent forms, case report forms, imaging data, and randomization allocation records for all subjects must be archived in a timely manner to ensure data integrity and traceability. Electronic data will be uploaded in real time through the central randomization system and the electronic data capture system and backed up to a dedicated server. Tiered authority management will be established to prevent unauthorized access and data leakage. After study completion, all paper materials will be uniformly organized and transferred to the storage location designated by the project leader, while electronic data will be stored and sealed on dedicated hard drives. According to GCP requirements, all study materials will be retained for at least 5 years after completion of the clinical trial for inspection by regulatory authorities. After the retention period expires, the materials will be destroyed according to relevant regulations and procedures, and the destruction process must be documented in writing and archived.

XIV. Study Costs

14.1 Funding Source and Financial Relationships

This study is funded by the National Science and Technology Major Project (Project No.: 2026ZD0554905). At the time this protocol was prepared, there were no obvious "potential conflicts of interest" that might affect the planning, implementation, statistical analysis, reporting, results, or interpretation of the study. Any "potential conflicts of interest" that may arise during the study will be appropriately managed by the investigators' institutions. In addition, implementation of the study will not harm the rights or interests of subjects.

14.2 Study Treatment Costs

Except for study drugs and devices, the remaining treatment and follow-up measures are routine treatment processes and follow-up requirements for this disease. Therefore, all medical expenses in this study will be covered by the patient's health insurance.

14.3 Compensation for Health Damage

If a patient experiences any health damage, appropriate treatment and care will be provided. If this study leads to death or sequelae, treatment will be provided within the scope of normal insurance care. The treatment costs for health damage will be covered by the patient's health insurance, and the patient will be responsible for the patient-share portion of expenses. No medical expenses or medical benefits will be provided.

Any adverse reaction or malfunction occurring in this study will be covered by clinical study liability insurance (policy number:).

XV. Study Quality Control and Assurance

1. Implementation of standard operating procedures

This study will develop standard operating procedures covering all key aspects, including subject screening and enrollment, the informed consent process, study drug and device management, implementation of interventions, adverse event management, and data recording and reporting. All research personnel must strictly follow the corresponding standard operating procedures when conducting study operations. Any deviation from the standard operating procedures must be recorded and explained. Before study initiation, the standard operating procedure documents will be uniformly distributed and training will be provided to ensure homogeneous operations across centers.

2. Investigator training

Before project initiation, a project initiation meeting and full investigator training meeting will be held to provide systematic training on the study protocol, standard operating procedures, operation of the central randomization system, standards for completing the case report form, and adverse event reporting procedures. For operation of the ischemic conditioning device, on-site demonstration and practical assessment will be conducted to ensure that each investigator is proficient in setting true/sham treatment modes and adjusting parameters.

3. Subject adherence management

Study-drug adherence will be assessed by pill counting. Subjects must return remaining drug boxes at each follow-up visit, and investigators will record the actual number of tablets taken. A count difference lower than 80% or higher than 120% will be considered poor adherence. The ischemic conditioning device has a built-in memory chip that can automatically record treatment frequency, time, and pressure parameters. Investigators will regularly export data to assess device adherence. At enrollment, investigators will explain in detail the significance of the study and key requirements

for cooperation. During follow-up, investigators will remind subjects of treatment and visit times by telephone or WeChat, and will appropriately affirm and encourage subjects with good adherence.

4. Study monitoring

This study will appoint independent clinical monitors to conduct regular monitoring. Monitoring will include: checking whether informed consent forms are signed properly; verifying consistency between case report form data and source documents; checking whether adverse events are recorded and reported completely and promptly; checking whether records of receipt and dispensing of study drugs and devices are accurate; and checking whether randomization operations comply with protocol requirements. The monitor will submit written monitoring reports, propose corrective actions for identified problems, and track implementation.

5. Data management

Data will be entered using an electronic data capture system. Data entry will be performed independently by two persons and compared for consistency to ensure accurate transcription. All data modifications will retain an audit trail to ensure traceability of data changes. After study completion, the data will be locked and exported for statistical analysis.

XVI. Data Safety Monitoring

A corresponding data safety monitoring plan will be developed for the clinical study according to the level of risk. All adverse events will be recorded in detail, properly managed, and tracked until properly resolved or until the condition is stable. Serious adverse events and unexpected events will be reported in a timely manner to the ethics committee, competent authority, sponsor, and drug regulatory authority according to the relevant systems. The principal investigator will regularly conduct cumulative reviews of all adverse events and, when necessary, convene investigator meetings to assess study risks and benefits. For studies involving more than minimal risk, independent data monitors will be arranged to monitor study data. For high-risk studies, an independent data safety monitoring committee will be established to monitor accumulated safety and efficacy data and make recommendations on whether the study should continue.

During the clinical trial, subjects' data shall be collected anonymously in the case report form. Subjects shall be identified only by subject number and initials of name in pinyin. If a subject's identity must be known because of safety or administrative instructions, the investigator and relevant personnel shall jointly bear confidentiality responsibilities. The informed consent form allows the patient to consent to direct access by authorized sponsors, ethics committees, and authorities to relevant source materials on the case report form, such as patient medical files, appointment records, and original laboratory records. These personnel shall comply with professional confidentiality rules and must keep all personal identifying information or medical information of patients confidential.

For blinded trials, the protocol shall specify the conditions for unblinding and the procedures for executing unblinding, and shall include emergency letters corresponding to the treatment codes. In emergencies, emergency unblinding of individual subjects is permitted to learn the treatment received, but the reason must be stated in the case report

form.

XVII. Trial Suspension or Termination

17.1 Individual Patient Discontinuation

17.1.1 Discontinuation criteria

When any of the following events occurs, the principal investigator or subinvestigator will discontinue the study for an individual patient:

1) The patient or the patient's legal representative withdraws consent to participate in the study;

2) The principal investigator or subinvestigator judges that it is difficult to continue the patient's participation in the study;

3) The principal investigator or subinvestigator judges that it is difficult to continue the study because of the patient's own reasons, such as failure to visit or inability to contact the patient;

4) The principal investigator or subinvestigator judges that the study should be discontinued because of a serious protocol deviation;

5) Any other situation in which the principal investigator or subinvestigator judges that the study should be discontinued.

17.1.2 Notes on discontinuation

1) The principal investigator or subinvestigator shall conduct discontinuation investigations according to the protocol as soon as possible. If investigation cannot be performed at the time of discontinuation because of patient-related reasons, the reason for discontinuation and the patient's health status, including adverse events and symptom course, shall be confirmed by telephone or other methods as far as possible.

2) The discontinuation date, detailed reason for discontinuation, such as adverse event or deterioration of the patient's condition, and investigation results at discontinuation shall be entered into the EDC as soon as possible.

3) If the reason for discontinuation is an adverse event, necessary investigations,

procedures, or treatment shall be performed until the adverse event resolves.

4) If the reason for discontinuation is deterioration of the patient's condition, necessary investigations, procedures, or treatment shall be performed.

5) The discontinuation date is the date of consent withdrawal specified in item 1) of "17.1.1 Discontinuation criteria"; in other cases, it is the discontinuation date determined by the principal investigator or subinvestigator.

17.2 Suspension or Interruption of the Overall Study

17.2.1 Considerations for continuation of the study

The study representative will consider whether to continue the study under any of the following circumstances:

1) When facts or information that impair the ethical validity or scientific rationale of the study are obtained:

a. Facts that impair "ethical validity of the study" refer to any facts that should be properly addressed during study implementation from the perspective of protecting human rights and considering patient welfare, including improper informed consent procedures or improper handling of personal information during study implementation.

b. "Facts that impair scientific rationale" refer to facts that may change the principal investigator's overall assessment of patient burden and expected risks and benefits stated in the study plan before study initiation, because of new scientific findings revealed after study initiation or information on contents and safety measures implemented by domestic or international regulatory authorities.

2) When facts or information that impair the appropriateness of study implementation or the reliability of study results are obtained:

a. Facts or information that impair "appropriateness of study implementation" refer to facts or information during study implementation that deviate from the policy for enrolling study patients or from study methods in the study plan.

b. "Facts or information that impair reliability of study results" refer to facts or information such as falsification or fabrication of study data.

3) When the expected risks during study implementation are judged to exceed the expected benefits;

4) When sufficient results have been obtained or when results cannot be obtained from the study.

Relevant information in items 1) to 4) shall be reported to the independent monitoring committee for review.

17.2.2 Notes on suspension or interruption

1) If the overall study is suspended, the study representative shall promptly report the reasons in writing to the principal responsible persons of participating hospitals. If the study is interrupted, the study plan shall be reviewed and the protocol revised if necessary. Any revision shall be promptly reported to the principal responsible persons of participating hospitals, and those persons shall restart the study according to the procedures of the participating hospitals.

2) The principal investigator or subinvestigator shall notify participating patients of the suspension or interruption and its reasons, and perform necessary investigations, procedures, or treatment.

17.3 Trial Termination

17.3.1 Individual patient trial termination

Termination of trial participation for an individual patient is defined as completion of the final investigation for the individual patient as specified in this protocol. The principal investigator shall promptly enter the end date and related information into the EDC after termination of the individual patient's study participation.

17.3.2 Overall trial termination

Overall trial termination is defined as the time when the statistical analysis manager submits the final analysis report to the study representative and the independent monitoring committee. After receiving the final analysis report, the study representative shall promptly prepare a study termination summary report and results summary for the principal responsible persons of participating hospitals.

XVIII. Study Organization Structure

18.1 Study Organization

● Principal Investigator

Professor Yan Zhang, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University

● Steering Committee

✓ The Steering Committee will provide scientific and strategic guidance for the trial and will have full responsibility for trial design,

implementation, and publication.

✓ The Steering Committee will ensure study quality, implementation, and management.

✓ The Steering Committee will approve the study protocol and operating guidelines before study initiation.

✓ The Steering Committee will hold regular teleconferences or face-to-face meetings to discuss and report study progress.

✓ The composition and responsibilities of the Steering Committee are described in the charter, and the final form will be determined before trial initiation.

● Executive Committee

The Executive Committee will review trial progress and collected available blinded data, and provide appropriate guidance for the study. Major decisions will be made through face-to-face meetings organized by the Executive Committee. The composition and responsibilities of the Executive Committee are described in the charter, and the final form will be determined before trial initiation.

● Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will regularly oversee the progress of

this study to ensure that the study meets

the highest standards of ethics and patient safety. It consists of academic members, including independent statisticians, who do not otherwise participate in the trial. DSMB qualifications will be documented by the DSMB and the Executive Committee before trial initiation, including membership, roles, and responsibilities. After each DSMB meeting, the report will be submitted immediately to the committee chair.

- Event Adjudication Committee

Clinical endpoint events, including stroke, progression, death, and major bleeding, as well as safety endpoints, will be reviewed by experts outside the trial, including neurologists and imaging specialists. Membership of the Event Adjudication Committee, including qualifications, roles, and responsibilities, shall be certified by the Event Adjudication Committee and the Executive Committee before trial initiation.

Neuroimaging for clinically relevant events will first be read at the subcenter, while the original imaging files will be submitted. The adjudication file will include the original imaging examination information.

18.2 Center Training and Certification

The Executive Committee shall ensure that all subcenters have received GCP training, and shall provide training to all subcenters on patient screening, follow-up, and outcome assessment, such as mRS scoring and MRI + MRA interpretation. Before study initiation, the principal investigators and coordinators of the subcenters shall complete training and obtain certification certificates as required.

Each center must complete project training and obtain certification before recruiting patients. The center PI and key study members will regularly participate in teleconferences to resolve problems encountered during the study. Certification will be issued by the training center.

The detailed study procedure manual will serve as the main reference document for

investigators. It will provide training guidance for investigators at study centers and will be updated regularly on the study website as needed throughout the study. Executive Committee members and study coordinators will communicate with center investigators by telephone, WeChat, or e-mail to resolve problems encountered during the study. The Executive Committee and the Monitoring Committee will jointly answer questions encountered or raised by subcenters, and will compile and distribute these questions and answers to all subcenters. Executive Committee members will manage and conduct on-site visits to subcenters to ensure the completeness and validity of data recorded in the case report forms. Each study center will be visited at least once during the trial, and additional visits will be conducted as needed if there are concerns about study data quality or subject enrollment.

XIX. Key Study Personnel

Name	Title / Specialty	Task	GCP Training (Time)
Yan Zhang	Chief Physician / Neurosurgery	Project leader; overall planning	February 2026
Qian Zhang	Chief Physician / Neurosurgery	Data monitoring and safety inspection	
Yahui Zhao	Attending Physician / Neurosurgery	Project manager; coordination and liaison	
Qingyuan Liu	Attending Physician / Neurosurgery	Data monitoring and safety inspection	
Qihang Zhang	Resident Physician / Neurosurgery	Project manager	February 2026
Chenyu Zhu	Resident Physician / Neurosurgery	Data collection	
Tong Liu	Resident Physician / Neurosurgery	Data collection	February 2026
Tongyu Yang	Resident Physician / Neurosurgery	Data collection	
Xingju Liu	Chief Physician /	Endpoint Event	

	Neurosurgery	Assessment Committee
Xudong Sun	Resident Physician / Neurosurgery	Endpoint Event Assessment Committee
Zihan Yin	Resident Physician / Neurosurgery	Endpoint Event Assessment Committee
Fanbo Meng	Resident Physician / Neurosurgery	Data monitoring and safety inspection
Hongqiu Gu	Research Fellow / National Clinical Research Center for Neurological Diseases	Methodology expert
Chunjuan Wang	Chief Physician / National Clinical Research Center for Neurological Diseases	Methodology expert
Xue Tian	Junior Title / Epidemiology and Health Statistics	Statistical guidance
Danlin Di	None / CRC	Randomization, device and drug management
Xinjie Liu	None / CRC	Follow-up

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Appendix 1 GUSTO Definitions

Appendix 2 Severity of Adverse Events (NCI-CTCAE 5.0 Criteria)

Adverse events will be assessed and graded according to NCI-CTCAE 5.0 as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; age-appropriate instrumental activities of daily living, such as preparing meals, shopping, using the telephone, and managing money, are limited.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; self-care activities of daily living, such as bathing, dressing and undressing, feeding, toileting, and taking medication, are limited, but the patient is not bedridden.
- Grade 4: Life-threatening; urgent intervention indicated.
- Grade 5: Death related to AE.

Note: A semicolon (;) in the grading description means "or."

Appendix 3 Method for Assessing the Modified Rankin Scale

The modified Rankin Scale is used to measure functional recovery outcomes after stroke. Bold text shows the formal definition of each level. Italic text provides further guidance to reduce possible interobserver variation, but it does not require a specific interview structure. Please note that only symptoms occurring after stroke should be considered. If a patient can walk without external assistance, even with the help of certain assistive devices, the patient is considered able to walk independently. If two levels seem equally applicable to the patient and further questioning is unlikely to produce an absolutely correct choice, the more severe level should be selected.

0 - No symptoms at all

Although there may be mild symptoms, the patient has not noticed any new functional limitation or symptom since the stroke.

1 - No significant disability despite symptoms; able to carry out all usual duties and activities

The patient has some symptoms caused by the stroke, whether physical or cognitive, such as effects on speech, reading, writing, movement, sensation, vision, swallowing, or emotion, but can continue all work, social, and leisure activities performed before the stroke. A key question to distinguish level 1 from level 2 below may be: "Are there things you used to do regularly that you can no longer do since the stroke?" Activities performed more than once per month are considered "usual."

2 - Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

Some activities that the patient could complete before the stroke, such as driving, dancing, reading, or working, can no longer be performed after the stroke, but the patient can still look after himself or herself daily without assistance from others. The patient can dress, walk, eat, use the toilet, prepare simple food, shop, and travel locally without help from others. The patient does not need supervision in daily life. A patient

at this level could be imagined as being able to stay alone at home for one week or longer without care.

3 - Moderate disability; requiring some help, but able to walk without assistance

At this level, the patient can walk independently, possibly with a walking aid, and can dress, use the toilet, and eat independently, but more complex tasks require assistance from others. For example, another person may need to shop, cook, or clean for the patient and visit more than once per week to ensure that these activities are completed. The assistance needed is not only physical care but more often advice; for example, a patient at this level may need supervision or encouragement to manage finances.

4 - Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

The patient needs another person to help with daily living, whether walking, dressing, toileting, or eating. The patient needs care at least once daily, usually twice or more, or must live close to a caregiver. To distinguish level 4 from level 5 below, consider whether the patient can routinely be alone for an appropriate period during the day.

5 - Severe disability; bedridden, incontinent, and requiring constant nursing care and attention

Although a trained nurse is not required, someone must check on the patient several times throughout the day and night.