RAPID local ischemic postconditioning in acute ischemic **S**troke p**A**tients recei**VE**d successful thrombectomy reperfusion (**RAPID-SAVE**)

STUDY PROTOCOL

Principal Investigator

Yueqi Zhu, MD

Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

Clinical Trial：NCT06526429

Protocol Version 2.0

Dec 23, 2024

PROTOCOL SIGNATURE PAGE

I have read this trial protocol and agree to adhere to the requirements.

I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational plan and the conduct of the study according to the Good Clinical Practices Guidelines and Institutional Review Board (IRB) requirements.

Clinical Site:_____

Site Principal Investigator Printed Name:_____

Site Principal Investigator Signature: _____Date:_____

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40 RAPID-SAVE Trial Protocol Synopsis

Title	RAPID local ischemic postconditioning in acute ischemic Stroke pAtients receiVEd successful thrombectomy reperfusion
Objective	To determine the safety and optimal dosage of RL-IPostC in AIS patients who have received successful thrombectomy reperfusion.
Study design	Bayesian Optimal Interval Phase I/II (BOIN12) trial design
Patient population	Patients with AIS and anterior circulation large vessel occlusion (LVO) who have undergone successful endovascular thrombectomy
Inclusion/Exclusion criteria	Inclusion Criteria: ① Age ≥ 18 years ② Presenting with symptoms consistent with acute anterior circulation ischemic stroke ③ Pre-stroke modified Rankin Score 0-1 ④ Baseline National Institute of Health Stroke Scale (NIHSS) score≥6 ⑤ Endovascular treatment can be initiated (femoral puncture) within 24 hours from stroke onset (stroke onset time is defined as last known well time) ⑥ Occlusion of the intracranial internal carotid artery, or the middle cerebral artery (MCA) (M1 or M2) and is the culprit artery ⑦ Ischemic core volume is < 70 ml, mismatch ratio >1.8 and mismatch volume is >15 ml as determined by CT perfusion imaging

	⑧ Embolism verified as the etiology of occluded artery ⑨ Modified Thrombolysis in Cerebral Infarction Score (mTICI) of 2b or 3 achieved after mechanical thrombectomy. ⑩ Time from CT perfusion to reperfusion < 2 hours ⑪ Informed consent signed Exclusion Criteria: ① Stenosis (≥50%) of the proximal MCA, internal carotid artery (ICA), or common carotid artery (CCA) of the culprit artery ② Presence of an ICA lesion that prevent the use of a balloon guide catheter ③ Multiple vascular embolisms on different pathways (e.g., bilateral MCA occlusions, or an MCA and a basilar artery occlusion) ④ Previous ischemic stroke within the past 3 months ⑤ Expected survival time of less than 6 months, precluding follow-up at 90 days (e.g., patient with malignant tumor) ⑥ Currently pregnant, mental disease, advanced hepatic or renal insufficiency, severe heart failure ⑦ Participation in other clinical trials that may confound the outcome assessment of this trial ⑧ Any other circumstances deemed inappropriate by the investigator for inclusion in this trial
Endpoints	Safety outcomes included the occurrence of malignant infarction, procedure-related serious adverse events, or other adverse events attributable to the procedure within 7 days.

	Efficacy was defined as the absence of clinically significant infarction lesion growth (>10 mL) from baseline to 72 hours.
Numbers of centers	Six investigational sites of national comprehensive stroke centers in China.
Sample size	A sum of 60 patients, organized into 12 cohorts, each consisting of 5 patients. The maximum sample size of each dosage level is capped at 20 patients.
Treatment	RL-IPostC procedure is administered immediately (within 5 minutes) following successful revascularization. A balloon guiding catheter placed properly at the ipsilateral C1 segment of ICA, inflated and deflated alternately to temporarily interrupt blood flow.

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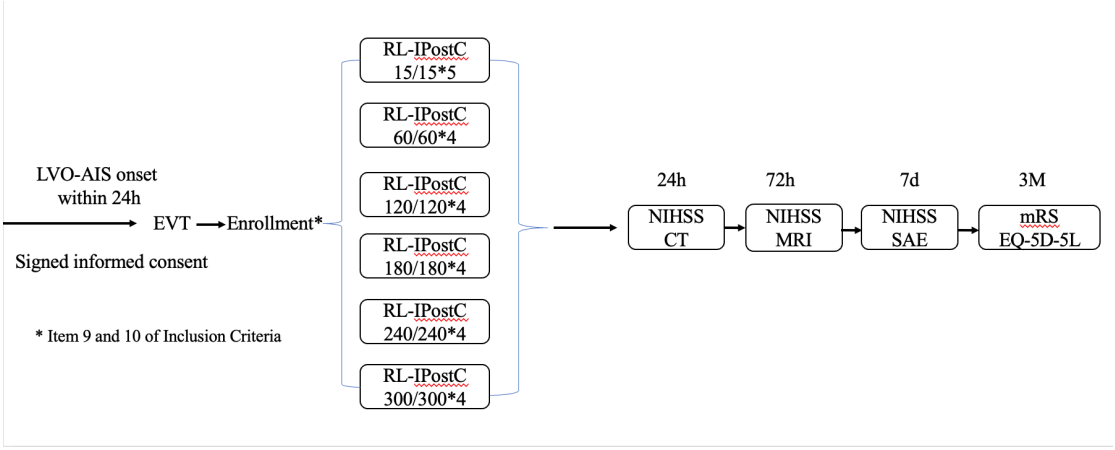
1. FLOWCHARTS

1.1 Graphical Study Design



LVO-AIS: large vessel occluded acute ischemic stroke. EVT: endovascular thrombectomy. RL-IPostC, Rapid local ischemic postconditioning. NIHSS: National Institutes of Health Stroke Scale. mRS: modified Rankin Scale. EQ-5D-5L: European Quality Five Dimension Five Level scale. SAE: serious adverse events.

1.2 Study Flowchart

Time points	Screen	Treatment	Follow up			
	-24 ~ 0h	0h	24 ± 12h	72 ± 24h	7d ± 24h	90 ± 7d
Demographic characteristics[1]	X					
Medical history[2]	X					
Concomitant medications	X	X	X	X		
Key time[3]	X	X				
Vital signs[4]		X	X	X		
Laboratory tests[5]	X					
Thromblysis[6]	X					
Multi-mode imaging[7]	X					

（NCCT+CTP+CTA）						
Postoperative imaging[8] (NCCT+MRI+MRA/CTA）			X	X	X	
Eligibility screen	X					
Informed consent	X					
Endovascular thrombectomy[9]		X				
sICH			X	X		
mRS [10]	X					X
NIHSS	X		X	X	X	
EQ-5D-5L						X
TOAST				X		
AE/SAE		X	X	X		X

1. Demographic characteristics: age, sex；

2. Medical history: including previous stroke, carotid artery disease, heart-related diseases, peripheral arterial disease, hypertension, diabetes, hyperlipidemia and other medical history, as well as high-risk factors such as smoking and alcohol history；

3. Key time: including "onset time", "arrival time", "CTP time", "femoral artery puncture time", "DSA first imaging time", "endovascular treatment vascular recanalization time", "BGC adaptation first filling time "；

4. Vital signs: including blood pressure, heart rate, temperature, and breathing；

5. Laboratory tests:

Red blood cell (RBC) count, white blood cell (WBC) count, neutrophil count, lymphocyte count, monocyte count, platelet (PLT) count, hemoglobin (Hb), creatinine（Cr）、Blood urea or urea nitrogen（BUN）、blood glucose（Glu）；prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR)；

6. Thrombolysis information: including drug name, infusion dosage and time, and occurrence of adverse events；

7. Imaging: multimodal CT (including cranial NCCT, CTP, CTA), if CTP can be used for cranial CTA reconstruction, CTA examination can be omitted;

8. Postoperative imaging: MRI must be done within 72± 24 hours. NCCT is completed 24 ± 12 hour, and other times as needed. MRA/CTA is completed within the follow-up time point and only needs

to be done once.

9. Information on thrombectomy treatment, including but not limited to: anesthesia method, thrombectomy product information, reperfusion results after the first thrombectomy and final angiography, and the number of final mechanical thrombectomy；

10. The mRS score of the selected group refers to the score before the onset of the disease.

11. EQ-5D-5L：European Quality of Life Five Dimension Five Level Scale Questionnaire.

2 BACKGROUND AND SIGNIFICANCE

Despite the well-established benefit of endovascular thrombectomy (EVT) in acute ischemic stroke (AIS) with large vessel occlusion (LVO), over half of patients remain functionally dependent at 90-day follow-up[1-4]. Efforts are increasing focus on understanding the reasons for poor outcome and factors limiting the efficacy of EVT[5]. Paradoxically, restoration of blood flow and reoxygenation can exacerbate tissue injury, known as 'reperfusion injury'[6,7]. This type of injury occurs immediately after blood flow restoration and is a major contribution to neurologic deterioration[8-10]. Recent clinical studies have confirmed that up to 37% of thrombectomy patients experience infarct lesion growth despite successful vascular recanalization, which is significantly associated with poor prognosis[11].

Ischemic postconditioning conventionally refers to a series of brief blood vessel occlusions and reperfusions, which may induce an endogenous neuroprotective effect and reduce cerebral ischemia/reperfusion injury[12]. It has demonstrated that remote ischemic postconditioning can improve 3-month functional outcomes in patients with moderate AIS[13,14], but this finding was not confirmed by other reports[15,16]. The delay of remote ischemic postconditioning initation after thrombolysis can't protect from the reperfusion injury. Rapid local ischemic postconditioning (RL-IPostC) , referring to the intervention promptly initiated after the onset of reperfusion that directly modulates the rapid augmentation of blood flow during reperfusion, may theoretically attenuate reperfusion injury. Previous reports have demonstrated neuroprotective effects in animal models of cerebral ischemia[17-20], yet remain unproven in clinical practice. With the widespread application of EVT for revascularization in LVO-AIS, RL-IPostC can

now be rapidly and conveniently implemented. Recent studies indicate that RL-IPostC is feasible and well-tolerated in AIS patients undergoing EVT, suggesting it could be a promising therapy to mitigate cerebral ischemia-reperfusion injury[21-23]. The most effective ischemic postconditioning protocol, has yet to be identified.

3 STUDY OBJECTIVES

To determine the safety and efficacy of RL-IPostC on LVO-AIS of successful thrombectomy, and the optimal dosage of RL-IPostC.

4 STUDY DESIGN AND MANAGEMENT OVERVIEW

4.1 Study design overview

The study is an investigator-initiated prospective, adaptive, multicenter clinical trial. It employs the Bayesian Optimal Interval Phase I/II (BOIN12) trial design to assess the safety and determine the optimal dosage of ischemic postconditioning intervention. The BOIN12 design facilitates decisions regarding dosage escalation and de-escalation by simultaneously taking account of toxicity and efficacy. It quantifies the desirability of a dosage in terms of toxicity-efficacy trade-off. Within the BOIN12 framework, patients are adaptively assigned to the most desirable dosage, balancing optimal toxicity and efficacy. The rank-based desirability score (RDS) can be pre-tabulated before the trial commences using the quasi-beta-binomial model[24]. In this trial, the following toxicity-efficacy trade-off utilities are established for calculating the RDS: (No Toxicity, Efficacy) = 100; (Toxicity, Efficacy) = 60; (No Toxicity, No Efficacy) = 40; (Toxicity, No Efficacy) = 0. The RDS table will be detailed in statistical analysis plan.

Stopping criteria are implemented to prevent the allocation of patients to dosage that is severely toxic or ineffective. BOIN12 utilizes two dosage-acceptability criteria to determine which dosage may be administered. If the probability of a toxicity outcome exceeding the upper limit of toxicity 0.15 is greater than 0.95, then dosage level and higher are eliminated from the trial. Conversely, if the probability of an efficacy

outcome falling below the lower limit of efficacy 0.60 is more than 0.90, then dosage level is removed from consideration. The dosage that is both admissible and has the highest estimated utility will be selected as the optimal dosage.

4.2 Blinding

Although the treatment medications are known to the patients and the treating neurointerventionist, the study employs a blinded assessment. Investigators responsible for follow-up neurological evaluations, as well as the independent Clinical Events Committee (CEC), are kept unaware of treatment group assignment to maintain objectivity. These assessors have no role in patient care.4.3 Study milestones

A 16-month budget and recruitment plan have been planned; the key study milestones are shown in the table below.

STUDY MILESTONES	
Pre-enrollment study initiation	2 months
Recruitment and follow-up	9 months
Completion of follow-up	3 months
Data analysis and publication	2 months
Total duration	16 months

This schedule is preliminary and may be adjusted based on the progress of the study.

4.4 Site recruitment

Six National Comprehensive Stroke Centers will be designated as trial sites. Selection will be based primarily on the following criteria: (1) prior experience in multicenter clinical trials; (2) an annual volume of no fewer than 50 endovascular thrombectomy procedures for AIS over the past three years; and (3) routine use of a balloon guide catheter in these procedures.

4.5 Site training, certification, and updates.

All investigators are required to complete the following training modules and receive certification:

- Study procedures
- Primer on the diagnosis of ischemic stroke.
- Rapid-SAVE eligibility
- Modified Rankin Scale score
- NIHSS

Successful completion of the training program and approval from the local Institutional Review Board (IRB) for human research will be required before a site can be certified to enroll patients. Intermittent web-based meetings with the principal investigator and key staff will be scheduled to address problems. A video of RL-IPostC conduction with BGC is recorded for interventionist training, reviewed in detail in the training modules. Case studies illustrating potential problems in adhering to the study protocol and blinding will be discussed. This will serve as a guide for training clinical site personnel and will be updated periodically throughout the study as needed.

An Executive Committee will be organized and periodically distribute a set of frequently asked questions and answers to the participating centers. Any queries regarding the study procedures during the study period will be addressed by the executive committee through calls or messages through Wechat.

4.6 Outcomes

The safety outcomes within 7 days, which are categorized as dosage-limiting toxicities (DLTs), including the following criteria: 1) Malignant MCA infarction, defined by a midline shift of ≥5 mm at the level of septum pellucidum, anisocoria due to herniation, or death resulting from herniation; 2) Complications associated with ischemic postconditioning intervention that necessitate treatment, including distal vascular embolism, local arterial dissection and vascular spasm at the intervention site of the ICA; 3) Serious adverse events (SAEs) that are causally linked to the intervention.

The efficacy outcome is defined by the reduction in infarction growth, measured as an infarction growth <10 mL from baseline to 72 hours post-intervention. Infarction volume will be evaluated using automate software analysis, which assesses baseline

CTP defined by relative cerebral blood flow (rCBF)＜30% and 72-hour diffusion-weighted imaging (DWI) or CT hypodensity volume.

5 PARTICIPANT SELECTION

All subjects will undergo a neurological and clinical assessment, routine laboratory blood test and baseline brain imaging. All these materials will be collected and screened by site physician. This includes standard of care use of non-contrast CT/ CT angiography/ CT perfusion. In order to track the potential for enrollment, screening log is required. Potential embolic LVO-AIS within 24 h of symptom onset ready for thrombectomy will be screened and signed informed consent if patients meet the inclusion and exclusion criteria except the item 9 and 10 of inclusion criteria. Before patient enrollment, all collaborating centers will obtain approval from the local IRBs or ethics committees which have access to all trial documents.

5.1 Inclusion and exclusion criteria

Inclusion Criteria:

① Age ≥ 18 years

② Presenting with symptoms consistent with acute anterior circulation ischemic stroke

③ Pre-stroke modified Rankin Score 0-1

④ Baseline National Institute of Health Stroke Scale (NIHSS) score≥6

⑤ Endovascular treatment can be initiated (femoral puncture) within 24 hours from stroke onset (stroke onset time is defined as last known well time)

⑥ Occlusion of the intracranial internal carotid artery, or the middle cerebral artery (MCA) (M1 or M2) and is the culprit artery

⑦ Ischemic core volume is < 70 ml, mismatch ratio >1.8 and mismatch volume is >15 ml as determined by CT perfusion imaging

⑧ Embolism verified as the etiology of occluded artery

⑨ Modified Thrombolysis in Cerebral Infarction Score (mTICI) of 2b or 3 achieved after endovascular thrombectomy.

⑩ Time from CT perfusion to successful reperfusion < 2 hours

⑪ Informed consent signed

Exclusion Criteria:

① Stenosis (≥50%) of the proximal MCA, internal carotid artery (ICA), or common carotid artery (CCA) of the culprit artery

② Presence of an ICA lesion that prevent the use of a balloon guide catheter

③ Multiple vascular embolisms on different pathways (e.g., bilateral MCA occlusions, or an MCA and a basilar artery occlusion)

④ Previous ischemic stroke within the past 3 months

⑤ Expected survival time of less than 6 months, precluding follow-up at 90 days (e.g., patient with malignant tumor)

⑥ Currently pregnant, mental disease, advanced hepatic or renal insufficiency, severe heart failure

⑦ Participation in other clinical trials that may confound the outcome assessment of this trial

⑧ Any other circumstances deemed inappropriate by the investigator for inclusion in this trial

5.2 Criteria for removal

Patients shall be withdrawn from the study after enrollment if either of the following protocol deviations occurs: (1) the RL-IPostC procedure is not initiated within 5 minutes after recanalization, or (2) the procedure is not completed as per the required dosage. However, termination of RL-IPostC due to patient intolerance will not warrant withdrawal; such cases must be adjudicated by the Clinical Events Committee (CEC) to determine if they constitute an RL-IPostC-related adverse event. All withdrawal cases will be documented in the case report form (CRF) and preserved for audit. Withdrawn patients will be excluded from the efficacy analysis.

5.3 Criteria for drop out

All patients enrolled in the trial will be retained until the completion of the follow-up. Subjects may request the withdrawal of informed consent and withdrawal from this study at any time without any reason, and their medical rights will not be affected. The investigator may also consider it medically necessary for the subject to discontinue the study. For subjects who withdraw from the study, their reason for withdrawal will be recorded, and the mRS score will be completed as far as possible before withdrawal.

5.4 Criteria for discontinuation of clinical studies

This study will provide an optimal balance between safety and efficacy according to pre-designed acceptable criteria, and the dosage will be abandoned or stopped once unacceptable safety and efficacy criteria are met.

6 TREATMENTS

RL-IPostC procedure is administered immediately (within 5 minutes) following revascularization. A balloon guiding catheter (BGC) is positioned at the ipsilateral C1 segment of ICA and is inflated and deflated to temporary stop antegrade blood flow. This study examines six dosages levels, with the initial dosage set at Dosage 3(2min/2min, 4 cycles). The dosing schedule is as follows:

① Dosage 1 (RL-IPostC 15/15, 5cycles): The intervention dosage consist of 15 seconds of occlusion followed by 15 seconds of reperfusion, repeated for 5 cycles.
② Dosage 2 (RL-IPostC 60/60, 4 cycles): The intervention dosage consist of 60 seconds of occlusion followed by 60 seconds of reperfusion, repeated for 4 cycles.
③ Dosage 3 (RL-IPostC 120/120, 4 cycles): The intervention dosage consist of 120 seconds of occlusion followed by 120 seconds of reperfusion, repeated for 4 cycles.
④ Dosage 4 (RL-IPostC 180/180, 4 cycles): The intervention dosage consist of 180 seconds of occlusion followed by 180 seconds of reperfusion, repeated for 4 cycles.
⑤ Dosage 5 (RL-IPostC 240/240, 4 cycles): The intervention dosage consist of 240 seconds of occlusion followed by 240 seconds of reperfusion, repeated for 4 cycles.
⑥ Dosage 6 (RL-IPostC 300/300, 4 cycles): The intervention dosage consisted of 300 seconds of occlusion followed by 300 seconds of reperfusion, repeated for 4 cycles.

7 SAFETY

7.1 Adverse events and management of SAEs

All adverse events occurring during the trial must be truthfully recorded in the adverse event table. The investigator should give targeted treatment and follow-up for adverse events until symptoms disappear or symptoms stabilize. In cases of serious adverse events, the investigator should take necessary treatment measures immediately to protect the safety of the subject when informed of the case.

7.2 Definitions of adverse events and severe adverse events

Adverse events: Any adverse medical occurrence from the time the subject signed the informed consent form to the last follow-up visit, regardless of whether there is a causal relationship with the trial treatment, is considered an adverse event. Adverse events that may occur during mechanical thrombectomy procedures usually include, but are not limited to: (1) Allergic reactions, (2) Puncture point bleeding, (3) Thromboembolic events, (4) Cerebral vasospasm, (5) Acute occlusion Possible causes, (6) Thrombosis and plaque shedding, (7) Blood vessel rupture, (8) Cerebral hyperperfusion syndrome.

Serious adverse events: Events requiring hospitalization, prolonged hospitalization, disability, affecting work capacity, endangering life or death, and causing congenital malformations during clinical trials. The following hospitalizations are not considered SAEs: Elective surgery already planned before signing the informed consent form; routine physical examination; hospitalization due to medical procedures not planned by the protocol; Elective admission to the hospital for stent implantation; Continued hospitalization for the purpose of neurorehabilitation therapy only.

7.3 Relationship to study treatment

RL-IPostC operation related adverse events are judged by CEC, including but not limited to distal vascular embolization within the territory, local arterial dissection, local vasospasm of the internal carotid artery requiring treatment, and large infarction growth due to delayed reperfusion. Treatment measures: Once the distal blood vessel embolism is blocked, antiplatelet drugs should be used immediately, thrombectomy should be performed if necessary, local arterial dissection should be observed in light cases, and stent implantation should be performed in severe cases.

7.4 AE Reporting

Once an adverse event (including serious adverse events) occurs, the time of occurrence of the adverse event, clinical manifestations, treatment process and duration, outcome and relationship with the drug should be recorded in detail on the case report form. If there are abnormal laboratory tests, the patient must be followed until the test results return to normal. Serious adverse events should be completed and reported to the investigator, the Ethics Committee (EC)within 24 hours after being notified.

The CEC consists of three experts, two neurointerventionists and a neurologist. The committee will assess all complications that occur during the course of the study and classify the severity and relevance according to the definitions in the Adverse Events (AEs) section. The CEC may request any relevant images and information required for the AE determination.

8 STATISTICAL CONSIDERATIONS

8.1 Sample size estimates

This maximum sample size of 60 and 12 cohorts, with a sample size of 5 for each cohort.

8.2 Statistical analysis plans

Details in supplementary material of statistical analysis plans (SAP).

8.3 Data safety monitoring plan

The independent Data and Safety Monitoring Board (DSMB) is composed of experienced two neurologists and one biostatistician who are neither directly involved in the study. The DSMB meets before the study initiation and during the study as required to reviews structured open-ended reports provided by research statisticians. The DSMB is responsible for making recommendations to the Executive Committee on the dosage escalation and deescalation, cessation or continuation of the study. In addition, the DSMB will review the occurrence of SAEs and make recommendations on the safety of the trial to continue, stop, or modify the study protocol.

9 ETHICAL AND REGULATORY STANDARDS

9.1 Ethical considerations

This clinical study must be conducted in accordance with the requirements of the Declaration of Helsinki and other relevant regulations. Before the study begins, the study protocol and informed consent form (ICF) and other documents must be approved by the Ethics Committee of the research center before the study can be conducted. Before each subject is selected for this study, the investigator should first give him or his legal representative a complete and comprehensive introduction to the purpose, procedures and possible risks of this study, and should let them know that they have the right to withdraw from this study at any time. The ICF shall then be signed by the subject or his/her legal representative and the investigator, and the signed ICF shall be kept as a clinical study document for future reference. Before the start of the clinical study, the investigator is required to submit the clinical study protocol, ICF and other

relevant documents to the Ethics Committee. Clinical studies can only be started after approval by the ethics committee. Any modifications to the study protocol must be approved by the Ethics Committee before implementation. SAEs that occur during the course of the clinical study should be reported in writing to the Ethics Committee within 24 hours of being informed by the investigator. The ethics committee of other clinical research centers participating in the study may review the feasibility of the study in the clinical research center by means of meeting review or document review, including the qualifications and experience of the investigator, equipment and conditions, etc., on the premise of accepting the review opinions of the ethics committee of the lead unit. The Ethics Committee will follow up and supervise the clinical research of the clinical research center, and may request the suspension or termination of the clinical study at any time in writing if it finds that the rights and interests of the subjects cannot be protected. Suspended clinical studies may not be resumed without the consent of the Ethics Committee. If SAE occurs in clinical research, the investigator should immediately take appropriate treatment measures for the subject and report in writing to the ethics committee of the clinical research center.

9.2 Informed consent

The investigator must provide the subject or his/her legal representative with an easy-to-understand informed consent form approved by the ethics committee and give the subject or his/her legal representative sufficient time to consider this study, and the subject shall not be enrolled until a signed written informed consent form is obtained from the subject. Subjects will be provided with all updated versions of informed consent along with written information during subject participation. Informed consent should be kept as an important document for clinical trials.

10 STUDY MONITORING

10.1 Site monitoring

During this study, a contract research organization (CRO) will organize and manage the

project, and a clinical monitor will be assigned to conduct regular on-site monitoring of the site, and the monitor should be allowed to evaluate data quality and study integrity. The ombudsman is responsible for cross-checking clinical study records with the subject's original medical records and working with the investigator to address any issues that arise during the trial. During the entire study period, the inspector was responsible for regularly checking the case report form (CRF), verifying the implementation and completion of the program, and ensuring the consistency and accuracy of the data filled in the form. The inspector can obtain the required laboratory test reports and medical records to verify the entry of pathology report forms.

10.2 Data collection

This study uses an electronic data capture (EDC) system to collect data, and the investigator should record all the data of each subject in the trial. Data will be entered into the electronic Case Report Form (eCRF) by the investigator or authorized clinical research site staff. Investigators and authorized clinical site staff will be properly trained and appropriate information security measures will be taken before clinical research site initiation or data entry. The investigator is responsible for maintaining all original documents and ensuring that they are monitored by a Clinical Research Associate (CRA) at each visit. In addition, the investigator is required to submit a complete eCRF for each participant enrolled in the study, regardless of the duration of the study. Study numbers and subject numbers submitted with the eCRF should be carefully verified and all personal privacy information (including subject names) should be deleted or made illegible to protect subject privacy.

10.3 Data management and quality control

In order to ensure the truthfulness, accuracy and reliability of clinical trial data and improve the quality of clinical data, the clinical monitor will review the completeness, consistency and accuracy of the trial data in accordance with the standard operating procedures during the trial project, and guide the personnel of the research institution to supplement and correct the problem data as necessary. The data manager writes a

program to check the data logically, including missing data, duplicate data, outliers, etc. The Clinical Ombudsman or Data Controller will raise the challenge in the form of an electronic challenge form, and the investigator or clinical research coordinator (CRC) must respond to the question and make corrections or explanations to the problem data, and if necessary, issue the challenge multiple times until the problem data is resolved. After cleaning, review and confirmation of data accuracy, the data will be locked and the locked data file will not be changed unless there are special circumstances.

11 PUBLICATIONS POLICY

The RAPID-SAVE study protocol and all related data and materials are confidential and are provided only to the investigator for the purpose of completing this study, and no content of this study protocol may be disclosed or disclosed to a third party without the prior written consent of the principal investigator. The RAPID-SAVE may provide data to other clinical investigators or government regulators as needed. All site investigators are obliged to provide the Steering Committee (SC)with all complete data collected during this study. At the end of the study, a writing committee will be established to review and publish the research data. The committee will consist of steering committee members and a subset of researchers. The writing committee will write/review abstracts and full-text manuscripts and select appropriate journals or conferences for publication. The RAPID-SAVE steering committee commits that data from the study will be published regardless of the study results and that the trial will be published on the clinical trial registry website.

Appendix 1 - Modified Rankin Scale[25]

Grade	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities

2	Slight disability：unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability： require some help, but able to walk without assistance
4	Moderate severe disability：unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	Severe disability：bedridden, incontinent, and require constant nursing care and attention
6	Death

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380 Appendix 2 -mTICI[26]

Grade	Description
0	No perfusion
1	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
2a	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (eg, in 1 major division of the MCA and its territory)
2b	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (eg, in 2 major divisions of the MCA and their territories)
3	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

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12 REFERENCES

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