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# Intensive blood pressure control after endovascular thrombectomy for acute embolic stroke (INTENSE): a multicentre, open-label, blinded-endpoint, randomized controlled trial

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Study Duration：2024.10.1-2026.09.30

Version Date：2024-08-03 Version Number：V1.0

**Abbreviation：**

| | |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| aSICH | Asymptomatic intracerebral hemorrhage |
| ASPECTS | Alberta Stroke Program Early CT Score |
| AST | Aspartate transaminase |
| CRF | Case record form |
| CT | Computed tomography |
| CTA | Computed tomography angiography |
| DSA | Digital subtraction angiography |
| EQ-5D | EuroQoL Group 5-dimension self-report questionnaire |
| mTICI | Modified thrombolysis in cerebral infarction |
| GFR | Glomerular filtration rate |
| ITT | Intention to treat |
| MRA | Magnetic resonance imaging angiography |
| MRI | Magnetic resonance imaging |
| mRS | Modified Rankin scale |
| NIHSS | National Institute of Health Stroke Scale |
| PP | Per-protocol |
| SAE | Serious adverse event |
| SICH | Symptomatic intracranial hemorrhage |

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## 1. Background

The latest findings from the Global Burden of Disease study indicate that China experiences 3.94 million new stroke cases annually, with a total of 28.76 million stroke patients, and 2.19 million stroke-related deaths each year [1]. Stroke is the third leading cause of death [2] and the primary cause of years lived with disability in China [1]. Among different subtypes of stroke, ischemic stroke accounts for the highest proportion, constituting 86% of stroke cases in individuals aged 40 and above [3], thereby placing a significant burden on both families and society.

Endovascular thrombectomy is one of the primary treatments for acute ischemic stroke due to large artery occlusion [2,3]. For acute anterior circulation large artery occlusion stroke, approximately 78%-96% of patients can achieve vessel recanalization through endovascular thrombectomy [4-8]. However, vessel recanalization does not equate to a good prognosis. The DIRECT-MT study found that the recanalization rates for direct thrombectomy and thrombectomy after intravenous thrombolysis within 4.5 hours of onset are 79.4% and 84.5%, respectively, while the good functional outcome rates are only 36.4% and 36.8% [5]. This mismatch suggests that solely pursuing vessel recanalization is insufficient to significantly improve clinical outcomes for stroke patients. Therefore, further researches on strategies to alleviate ischemia-reperfusion injury, based on vessel recanalization, holds the potential to overcome challenges in this field and provide new perspectives for the treatment of acute anterior circulation large artery occlusion stroke.

Blood pressure is a critical clinical management parameter that is closely linked to the prognosis of stroke patients. Observational studies suggest that elevated blood pressure is associated with worse functional outcome at 3 months in acute ischemic stroke patients undergoing thrombectomy [9-13]. Recent meta-analyses have demonstrated that high 24-hour mean systolic blood pressure following mechanical thrombectomy is correlated with both 3-month functional impairment and mortality [14, 15]. Currently, several randomized controlled trials have been conducted to investigate the optimal blood pressure management targets following intravascular therapy in patients with anterior circulation stroke. The results of the BP TARGET study [16] indicated that a greater reduction in systolic blood pressure within 24 hours following endovascular treatment was associated with better prognosis. However, no significant difference in 3-month outcomes was observed between the intensive SBP target group (systolic blood pressure between 100-129 mmHg

within 24 hours after successful endovascular therapy) and the standard SBP target group (systolic blood pressure between 130-185 mmHg within 24 hours after successful endovascular therapy). In this study, the difference in blood pressure between the intensified hypotension and standard blood pressure groups was relatively modest (average systolic blood pressure within 24 hours was 128 mmHg and 138 mmHg, respectively), which may have been insufficient to detect the potential benefits of a further reduction in systolic blood pressure. On this basis, the ENCHANTED2/MT study [17] employed a grouping strategy with more pronounced differences in blood pressure and found that, compared to the less intensive treatment group (systolic blood pressure between 140-180 mmHg within 72 hours), the more intensive treatment group (systolic blood pressure <120 mmHg within 72 hours) exhibited a higher proportion of poor functional outcome at 3 months. However, no significant differences were observed between the two groups in terms of symptomatic intracranial hemorrhage or 3-month mortality [17]. The recently published OPTIMAL-BP study [18] reached a conclusion consistent with that of the ENCHANTED2/MT study: the three-month poor functional outcome rate in the intensive management group (systolic blood pressure <140 mmHg within 24 hours) was significantly higher than that in the conventional management group (systolic blood pressure between 140-180 mmHg within 24 hours). Additionally, no significant differences were observed in the incidence of symptomatic intracranial hemorrhage or in the three-month stroke-related mortality between the two groups. The results of the BEST-II study [19], published almost simultaneously, demonstrated that lower SBP targets less than either 140mmHg or 160mmHg after successful endovascular therapy did not meet prespecified criteria for futility compared with an SBP target of 180mmHg or less. Therefore, it cannot be concluded that lower postoperative blood pressure targets are harmful [19]. In summary, existing studies present inconsistent recommendations regarding blood pressure management following successful reperfusion with endovascular thrombectomy, likely due to differences in populations, interventions, and other factors. Further precise researches are necessary to better define the optimal strategy.

The aforementioned randomized controlled trials did not fully account for the impact of stroke etiology on the results. Atherosclerosis and embolism are the two most common causes of acute ischemic stroke [20]. Patients with large large-artery atherosclerotic stroke often have long-term atherosclerotic stenosis of vessels, which promotes collateral circulation, resulting in better

collateral circulation compared to embolic stroke patients [21-23]. Studies have indicated that blood pressure variability following vascular recanalization is linked to prognosis in patients with poor collateral circulation, but not in those with good collateral circulation [24-26]. Thus, patients with embolic strokes may be more susceptible to the effects of blood pressure. A recent study confirmed this view by analyzing blood pressure data from 147 patients with atherosclerotic stroke and 273 patients with cardioembolic stroke [27]. The study found that in patients with cardioembolic stroke, greater blood pressure variability within 24 hours after endovascular therapy was associated with a lower risk of functional independence at 3 months and a higher risk of cerebral hemorrhage. However, these correlations were not observed in patients with atherosclerotic stroke [27]. After acute ischemic stroke, impaired cerebral autoregulation makes blood flow in penumbra highly sensitive to blood pressure [28]. Elevated blood pressure can increase cerebral perfusion pressure and induce microvascular dilation, which may trigger microvascular spasm, further damage the blood-brain barrier, and convert ischemic vessels into channels for cerebral edema and hemorrhagic transformation [15, 29]. Conversely, excessively low blood pressure can result in inadequate cerebral blood flow, causing hypoperfusion, enlarging the infarct, and contributing to a poor prognosis [30]. After endovascular thrombectomy, patients with large-artery atherosclerotic stroke often have residual stenosis. Intensive blood pressure control in these patients may lead to hypoperfusion and exacerbate ischemic symptoms, thus blood pressure should be maintained at a relatively higher level. In contrast, for patients with embolic stroke, as there is no residual stenosis in the vessels, the primary concern after vascular recanalization is preventing hyperperfusion-related hemorrhagic transformation, and blood pressure should be kept at a relatively lower level. Compared to patients with large artery atherosclerotic stroke, those with embolic stroke may require more stringent blood pressure management. Previous studies that directly pooled patients with different stroke etiologies may have masked the impact of blood pressure on prognosis.

Therefore, we proposed a multicenter randomized controlled trial to investigate the impact of early intensive blood pressure control on the prognosis of patients with embolic stroke after successful reperfusion following endovascular thrombectomy.

## 2. Objectives

To investigate the safety and efficacy of intensive blood pressure control after successful

reperfusion following thrombectomy in patients with acute anterior circulation large artery embolic stroke.

**3. Design**

The study employs a multicenter, prospective, randomized, endpoint-blinded, parallel-controlled trial design. Patients with acute anterior circulation large artery occlusive stroke, who receive successful reperfusion after endovascular thrombectomy within 4.5 or 6.0 hours of onset, without significant in-situ or proximal vessel stenosis, and with sustained elevated systolic blood pressure (≥140 mmHg for >10 minutes), will be enrolled according to the clinical inclusion and exclusion criteria. The enrolled patients will be randomly assigned to the experimental group or control group (1:1). The experimental group will undergo intensive blood pressure management (target systolic pressure <120 mmHg, achieved and maintained within 1 hour for 48 hours), while the control group will have less intensive blood pressure control (target systolic pressure 140-180 mmHg). Patients will be followed up for 3 months to assess their prognosis.

**4. Patient selection**

**4.1 Inclusion criteria**

Age ≥ 18 years;

To receive endovascular thrombectomy <24 hours after the onset of symptoms；

Diagnosed with acute anterior circulation ischemic stroke;

National Institutes of Health Stroke Scale (NIHSS) score ≤ 30;

Alberta Stroke Program Early CT Score (ASPECTS) ≥ 6;

Computed Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA), or Digital Subtraction Angiography (DSA) confirming occlusion of the intracranial internal carotid artery or M1/M2 segment of the middle cerebral artery;

Successful recanalization of the occluded vessel without in-situ or proximal stenosis (modified Treatment in Cerebral Infarction, mTICI ≥ 2b);

Sustained elevated systolic blood pressure (≥140 mmHg for at least two consecutive measurements, separated by >10 minutes) within 3 hours of reperfusion;

Written informed consent provided by the patient or their legal representative.

**4.2 Exclusion criteria**

Pre-existing stroke disability defined by a modified Rankin score (mRS) >2；

Unlikely to benefit from or tolerate endovascular thrombectomy, such as severe allergic reaction to contrast agents;

Failure to achieve mTICI ≥ 2b with endovascular intervention, or presence of in situ or proximal vascular stenosis;

Patients with contraindications for the use of antihypertensive medications, such as allergy to components;

Intracranial space-occupying lesions, including brain tumors and vascular malformations;

Patients with severe liver or renal dysfunction, or those receiving dialysis (severe liver dysfunction is defined as alanine aminotransferase [ALT] > 3 times the upper limit of normal or aspartate aminotransferase [AST] > 3 times the upper limit of normal; severe renal dysfunction is defined as serum creatinine > 3.0 mg/dL [265.2 μmol/L] or glomerular filtration rate [GFR] < 30 mL/min/1.73 $m^2$)；

Serious illness with life expectancy of <6 months;

Lactating women;

Participation in other interventional clinical trials within the past 3 months;

Any other conditions that render patients unsuitable for participation in this study or unable to complete the study process, such as psychiatric disorders, cognitive or emotional impairments, or physical conditions that hinder compliance with study procedures and follow-up.

**4.3 Criteria for withdrawal**

The study should be terminated if any of the following conditions occur:

Voluntary withdrawal, participants can freely withdraw at any time;

Deliberate or inadvertent non-compliance with the study procedures;

Any other circumstances where the investigator deems that continuing the study would harm the patient's health;

Patients can withdraw from the study at any stage for any reason. Similarly, the investigators have the right to terminate a patient's participation in case of an emergency medical condition. For patients who withdraw, the investigator must inquire about the reason for withdrawal and whether any adverse events (AE) occurred. If the withdrawal is due to an AE, follow-up should be conducted

until the AE is resolved, unless the investigators deem that the condition is due to the patient's underlying disease and is unlikely to resolve. The reason for withdrawal and the date must be recorded in the case report form (CRF).

**4.4 Criteria for dropout**

Patients who are unable to complete the 3-month follow-up due to subjective or objective reasons.

**4.5 Privacy protection**

Patients' medical records (study case records/CRFs, laboratory reports, etc.) will be securely stored at the hospital, with clinical test results well documented. Only the researchers involved in this study, the ethics committee, and regulatory authorities will be permitted to access the patient's medical records. Any public reports on the study findings will not disclose any patient identifying information. We will make every effort, within the bounds of the law, to protect the privacy of patients' medical data. In accordance with medical research ethics, except for personal privacy information, trial data will be accessible for public inquiry and sharing, limited to web-based electronic databases.

**5. Sample size calculation**

Based on published literature and clinical experience, the estimated 90-day functional independence rate (defined as mRS $\leq 2$) in the control group is 35%. Using a two-tailed significance level of $\alpha = 0.05$, with 80% statistical power ($1-\beta = 0.8$), and a 1:1 allocation ratio between the experimental and control groups, we estimate that 376 participants per group are needed to detect a 10% improvement in the functional independence rate between groups. Considering a 20% dropout rate, a total of 910 subjects are needed to be enrolled, with 455 participants in each group.

Randomization will be performed using block randomization with block size of 10 (with at least 10 participants per center). For practical implementation, each center will be allocated a block, for example, if Center 1 plans to enroll 20 participants, blocks 1-2 will be allocated. This randomization scheme will be followed accordingly. If stratification variables are used, randomization will be performed within each stratum.

**6. Randomization**

Patients will be randomly assigned to two groups in a 1:1 ratio. Stratified block randomization will be used, with stratification by study center and intravenous thrombolysis. A 1:1 randomization

sequence will be generated. The randomization process will be managed using the "Jinling mouse" app.

**7. Medication protocol**

Blood pressure will be continuously monitored using a noninvasive device applied to the nonparalyzed arm or the right arm. The measurement intervals are as follows: every 15 minutes within the first hour post-randomization, every hour from 2 to 6 hours, every 6 hours from 4 to 24 hours, and then twice daily until day 7 (if the patient is discharged or dies before day 7, monitoring will be discontinued).

Given the clinical uncertainties regarding the potential benefits and risks, this study encourages adherence to the protocol but allows for adjustments to the treatment plan based on clinical needs. Nicardipine is recommended for blood pressure management, but other antihypertensive medications may be also selected according to the clinician's judgment.

Nicardipine injection administration protocol: dilute with saline or 5% glucose injection to prepare a solution containing 0.01–0.02% nicardipine hydrochloride (0.1–0.2 mg per 1 mL). Administer by intravenous infusion, starting at a rate of 2–10 μg/kg body weight per minute. Once the target blood pressure is achieved, adjust the infusion rate while continuously monitoring blood pressure. If necessary, intravenous administration can be increased to a dose of 10–30 μg/kg body weight per minute.

**7.1. Intensive blood pressure control group (experimental group)**

The target blood pressure is <120 mmHg within 1 hour after randomization, and this level should be maintained for at least 48 hours. Intravenous antihypertensive treatment should begin immediately after randomization. A systolic pressure of 100 mmHg is the threshold for discontinuing both antihypertensive and vasopressor therapy. Oral antihypertensive agents may be used once blood pressure stabilizes. Care should be taken to avoid the occurrence of hypotension.

**7.2. Less intensive blood pressure control group (control group)**

The target blood pressure is 140-180 mmHg within 1 hour after randomization, and this level should be maintained for at least 48 hours. Intravenous antihypertensive therapy is preferred. Antihypertensive agents should be used intravenously when systolic pressure exceeds 180 mmHg, and discontinued when systolic pressure is ≤150 mmHg. Oral antihypertensive agents may be used

once blood pressure stabilizes. Even if systolic pressure drops below 140 mmHg, vasopressors should not be used unless hypotension occurs.

## 8. Outcomes

### 8.1 Primary efficacy outcome

Functional independence (90-day mRS score ≤ 2).

### 8.2 Primary safety outcomes

Rate of symptomatic intracranial hemorrhage (sICH), defined by the Heidelberg Bleeding Classification criteria [31];

All-cause mortality at 3 months.

### 8.3 Secondary efficacy outcome

mRS score 0–1 at 90 days;

mRS score 5–6 at 90 days;

Functional recovery, defined by 90-day mRS score improvement (shift analysis);

Infarct volume at 24 hours;

Change in infarct volume at 24 hours (compared to baseline);

NIHSS score at 24 hours;

Change in NIHSS score at 24 hours (compared to baseline);

24-hour NIHSS score 0–1 or improvement >8 points (%);

Change in NIHSS score at 7 days;

Brain edema volume at 7 days;

Health-related quality of life at 90 days (assessed by EQ-5D score).

### 8.4 Secondary safety outcomes

Asymptomatic intracerebral hemorrhage (aSICH);

Large cerebral infarction or surgical intervention for intracerebral hemorrhage;

Complications excluding intracerebral hemorrhage (including gastrointestinal bleeding, urethral bleeding, oral or nasal mucosal bleeding, and subcutaneous hematomas);

Non-hemorrhagic severe adverse events (including brain herniation, pneumonia, respiratory failure, circulatory failure, stress ulcers, secondary epilepsy, urinary tract infections, sepsis, renal failure, acute coronary syndrome, venous thromboembolism, and psychiatric symptoms);

Procedure- or device-related complications (including arterial rupture, arterial dissection, complications at the vascular puncture site, and vasospasm).

**9. Statistical analysis**

**9.1 Statistical analysis populations**

Intention-to-Treat (ITT) Population: This population will include all randomized patients, regardless of whether they receive the intended intervention. A modified ITT analysis will be conducted based on the principle of the closest approach to the ITT population. Patients who withdraw consent before the blood pressure intervention, do not undergo the assigned procedure after randomization, lack endpoint data, refuse follow-up, or are lost to follow-up will be excluded from the statistical analysis. The modified ITT analysis will be used to evaluate the effectiveness and safety of the treatment regimen.

Per-Protocol (PP) Population: This population will exclude all patients with significant protocol violations, such as those who are under 18 years of age, have a final diagnosis other than acute ischemic stroke, have sustained systolic blood pressure <140 mmHg post-surgery, do not achieve reperfusion (mTICI <2b), have a pre-stroke mRS score of 3-5, lack 3-month follow-up data, or do not achieve the expected blood pressure control. The PP analysis will serve as a supplement to the modified ITT analysis.

**9.2 Statistical analysis methods**

For continuous variables that follow a normal distribution, data will be presented as mean ± standard deviation. For continuous variables that do not follow a normal distribution, data will be presented as median and interquartile range. Between-group comparisons will be performed using the independent t-test or Mann-Whitney U test. Categorical or ordinal data will be summarized using frequencies and percentages. For comparisons of categorical data between two groups, the $\chi^2$ test or Fisher's exact test will be used; for ordinal data, the Mann-Whitney U test will be applied. All statistical analyses will be performed using SPSS software. A p-value < 0.05 will be considered statistically significant.

**10. Study steps**

After preliminary screening, patients who meet the criteria for endovascular intervention will undergo the procedure. Endovascular treatment methods include mechanical thrombectomy and aspiration.

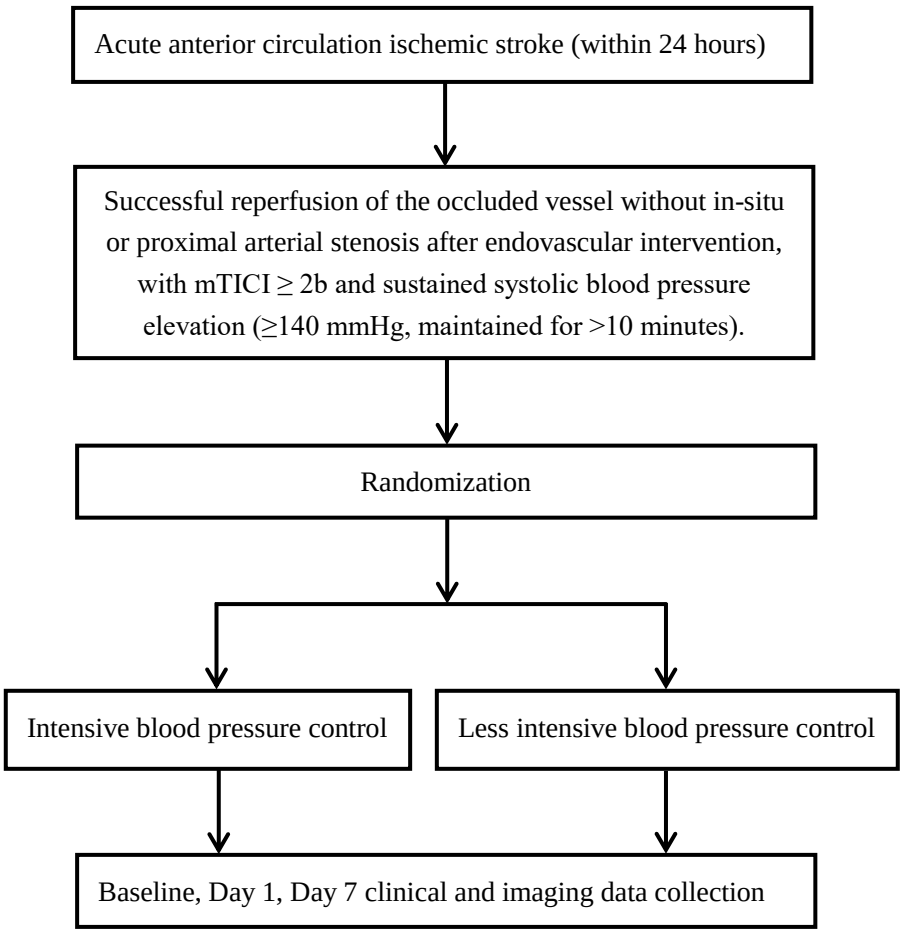
At the end of the endovascular procedure, angiography will be used to assess successful reperfusion of the occluded vessel without in-situ or proximal arterial stenosis, with mTICI ≥ 2b. Additionally, the patient's systolic blood pressure will be continuously elevated (≥140 mmHg, maintained for >10 minutes).

Randomization.

The intensive blood pressure control group will receive more intensive blood pressure management (target systolic blood pressure of 120 mmHg, achieved within 1 hour and maintained for 48 hours). The less intensive blood pressure control group will not have strict blood pressure control (target systolic blood pressure of 140-180 mmHg).

Follow-up and data collection.

**11. Study schema**



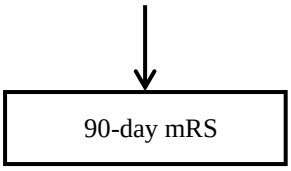



Figure 1. Study schema

**12. Schedule of evaluations**

| Evaluation | Baseline (Prior randomisation) | Treatment phase | | Follow-up phase |
|---|---|---|---|---|
| | | 1 day | 7 days[a] | 90 days |
| Consent | X | | | |
| Eligibility | X | | | |
| Basic information | X | | | |
| Medical history | X | | | |
| Blood pressure | X | X | X | |
| mRS | X | | X | X |
| NIHSS | X | X | X | |
| ASPECTS | X | | | |
| EQ-5D | | | | X |
| Blood tests | X | | | |
| Menstrual history/urine pregnancy test (female) | X | | | |
| Electrocardiogram | X | | | |
| Details of rt-PA (if performed) and endovascular thrombectomy | X | | | |
| Brain imaging (CT ± CTA/MRI±MRA/DSA) | X | X | X | |
| BP lowering treatment | | X | X | |
| Standard stroke care | | X | X | X |

| | | | | |
|---|---|---|---|---|
| SAEs | X | X | X | X |
| Complications | | X | X | X |
| Completion status of research | | | | X |

Table 1. Experimental procedures and items to be assessed at each time point

a：Or the day of discharge (if the patient is discharged before day 7).

**13. Management of adverse events during and after the study**

**13.1 Adverse event (AE)**

An AE refers to any unfavorable medical event that occurs in a participant after receiving a drug or medical device, but it is not necessarily causally related to the treatment.

**13.2 Severity assessment of AEs**

The intensity or severity of AEs is categorized into four levels:

- Mild: Does not affect daily activities.
- Moderate: Affects daily activities.
- Severe: Results in the loss of ability to perform daily activities.
- Serious: As defined by the serious adverse event (SAE) criteria.

**13.3 SAEs**

An SAE refers to any event occurring during the clinical trial that results in:

- Death;
- Severe deterioration in the health of the patients, users, or others;
- Life-threatening illness or injury;
- Permanent impairment of bodily structure or function;
- Requirement for hospitalization or prolongation of hospitalization;
- Need for medical or surgical intervention to prevent permanent impairment of body structure or function, fetal distress, fetal death, or congenital abnormalities/defects.

Note: Hospitalization planned due to pre-existing conditions or as required by the clinical trial protocol, without significant deterioration in health, is not considered an SAE.

**13.4 AEs reporting**

Any AE occurring during the trial will be reported by the investigators and clinical sites to the relevant national and local regulatory authorities within the specified timeframes, in accordance with national regulations. The investigators will assist the regulatory authorities in investigating the AE and implementing appropriate corrective and preventive measures.

Any SAE occurring during the clinical study must be reported by the investigator to the study's ethics committee and the clinical research sponsor within 24 hours of becoming aware of the event. Additionally, the investigator must complete a serious adverse event form, documenting the time of occurrence, severity, duration, measures taken, and outcome.

The investigators should follow up and record the outcomes of all AEs, tracking patients who withdraw from the study due to an AE until the AE is fully resolved. The investigator must assess whether the AE is related to the study intervention and provide supporting evidence for this assessment. Any clinically significant abnormal findings in clinical or laboratory tests should be recorded on the adverse event form, with follow-up observations at least once a week until the condition normalizes or returns to baseline levels.

Researchers should follow up on all adverse events (AEs) to observe and record their outcomes, and track patients who withdraw from the study due to an AE until it is fully resolved. Researchers must assess whether the AE is related to the research intervention and provide supporting evidence for this assessment. All clinically significant abnormalities in clinical or laboratory tests should be documented in an AE form and monitored during follow-up, with observations conducted at least weekly until normal or baseline levels are restored.

**14. Follow-up and medical measures after study completion**

The patients will be followed up within 3 months after discharge and continue long-term secondary prevention treatment for cerebral infarction.

**15. Data retention**

The CRF is prepared in triplicate: one copy is retained by the sponsor, one by the participating institution, and one by the statistical unit. Demographic data, relevant medical history, physical examinations, laboratory test results, concomitant medications, and adverse events are recorded in the CRF as raw data, with any information related to the subject's privacy documented only in the original medical records.

Researchers must store research documents securely according to relevant guidelines. Key documents should be retained for 5 years after the completion of the clinical study. After this period, the investigator should promptly contact the sponsor to discuss the handling of the study materials.

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