Statistical Analysis Plan

Title of Clinical Study Protocol:	Endovascular Treatment for Mild Ischemic Stroke Caused by Acute Anterior Circulation Large Vessel Occlusion: A Multicenter Prospective Randomized Controlled Clinical Trial (MILD-MT)
Version of Clinical Study Protocol:	V1.0
Date of Clinical Study Protocol Version:	November 8, 2023
ClinicalTrials.gov register Identifier:	NCT06179017
Sponsor:	Zhangzhou Affiliated Hospital of Fujian Medical University
Statistical Analysis Unit：	Peking University Clinical Research Institute
Version of Statistical Analysis Plan:	V1.0
Date of Statistical Analysis Plan Version:	April 25, 2026

Study identifiers

- Protocol Version:V1.0, November 8, 2023
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Revision history

Version	Date	Details
V1.0	April 25, 2026	Final version

Contributors to the statistical analysis plan

- Roles and responsibilities

Name	Affiliation	Role on study	SAP contribution
Professor Jianmin Liu	Cbanghai Hospital, Shanghai, China	General consultant	Be responsible for the overall direction and design of the study to ensure the orientation of the study protocol and the SAP
Professor Wenhuo Chen	Fujian Medical University Union Hospital,Fuzhou, China	Co-Principal Investigator	Reviewed all SAP versions
Professor Zeguang Ren	Affiliated Hospital of Guizhou Medical University, China	Co-Principal Investigator	Reviewed all SAP versions
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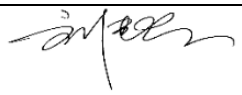
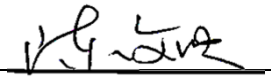
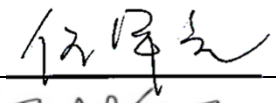
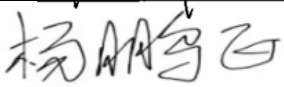
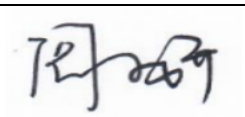
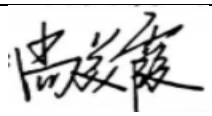
- Approvals

The undersigned have reviewed this plan, approve it as final and as consistent with the requirements of the protocol as it applies to their respective areas. They also confirm that this analysis plan was developed in a completely blinded manner, that is without knowledge of the effect of the intervention(s) being assessed.

- Signature

Name	Signature	Date
Professor Jianmin Liu		April 25, 2026
Professor Wenhuo Chen		April 25, 2026
Professor Zeguang Ren		April 25, 2026
Professor Pengfei Yang		April 25, 2026
Professor Tingyu Yi		April 25, 2026
Professor Xiaoyan Yan		April 25, 2026
Professor Meixia Shang		April 25, 2026

Directory

1. Description

This Statistical Analysis Plan (SAP) aims to describe the statistical analysis methods and processes adopted in the clinical trial evaluating the safety and efficacy of endovascular treatment for mild ischemic stroke caused by acute anterior circulation large vessel occlusion. It applies to the statistical analysis after database locking of this study. This SAP complies with the provisions of the International Council for Harmonisation (ICH) E9 guideline "Statistical Principles for Clinical Trials", and is confirmed to be developed under full blinding, —that is, without knowledge of the effects of the assessed intervention (or combination of interventions). This SAP is developed based on Clinical Study Protocol V1.0 (Date: November 8, 2023). This SAP may be revised following revisions to the Clinical Study Protocol.

2. Study Overview

2.1. Study Objectives

To explore the efficacy and safety of endovascular treatment compared with the best medical treatment in mild stroke patients due to anterior circulation LVO. Eligible patients have confirmed intracranial carotid artery (ICA), middle cerebral artery (MCA M1/M2) segment with or without ipsilateral extracranial ICA occlusion, symptom onset within 24 hours, small core infarct (≤50 ml), and substantial perfusion mismatch (≥50 ml), a profile indicating high risk for early neurological deterioration.

2.2. Study Design

MILD-MT trial is a multicenter, prospective, randomized, open-label, blinded endpoint (PROBE) trial designed to evaluate whether EVT combined with best medical management (EVT+BMM) is superior to BMM alone in mild stroke patients due to anterior circulation LVO. The intervention Group (EVT+BMM) will receive endovascular therapy, while the control group(BMM) will receive the best medical treatment. The study will last for approximately four years in total.

2.3. Follow-up Plan

The follow-up period for this clinical study is 90±7 days, with a total of 4 follow-up visits. Three of the visits(on the day of randomization, at 48±24 hours after randomization, and at 7±1 days after

randomization) will be completed at the study site. The visit at 90±7 days after randomization may be conducted either as an on-site follow-up at the hospital or via telephone follow-up. The follow-up should be performed with the patient themselves or a co-residing caregiver. The follow-up assessor must be a researcher at the research center who is blinded to the subject's treatment group allocation.

3. Study Population

3.1. Inclusion Criteria

1) Age 18-80 years;

2) Symptoms onset or last known well to randomization is within 24 hours;

3) Clinical diagnosis of acute ischemic stroke due to anterior circulation intracranial large vessel occlusion (LVO) (including intracranial internal carotid artery [ICA], middle cerebral artery [MCA] M1 segment, MCA M2 segment, with or without ipsilateral extracranial ICA occlusion) confirmed on Computerized tomography angiography (CTA) or Magnetic resonance imaging angiography (MRA)；

4) Baseline NIHSS score <6 before randomization (including cases with NIHSS≥6 at onset but improves before randomization);

5) ASPECTS score ≥ 6 based on Non-contrast CT (NCCT) before randomization, and computerized tomography perfusion (CTP) or magnetic resonance imaging perfusion (MRP) imaging presented infarct core volume (relative cerebral blood flow (rCBF) <30%/DWI-ADC＜620) ≤50ml, and mismatch volume (Tmax>6 seconds volume - rCBF <30% /DWI-ADC＜620) ≥50ml；

6) Patients or their legal representatives voluntarily signed the informed consent form.

3.2. Exclusion Criteria

3.2.1. Clinical Exclusion Criteria

1) Premorbid Rankin Scale (mRS) score≥1;

2) Known allergy to iodine, heparin, anaesthesia, or other definite contraindication to receiving endovascular treatment (EVT) procedure;

3) Patient has severe or fatal co-morbidities that could interfere with outcome assessments and follow-up (such as malignant tumor, severe heart failure, or renal failure, or life expectancy less than 6 months);

4) Poorly controlled hypertension (systolic blood pressure >220mmHg or diastolic blood pressure >120 mmHg);

5) Baseline blood glucose <50mg/dL(2.78 mmol/L) or >400mg/dL(22.20 mmol/L);

6) Known bleeding tendencies, including but not limited to platelet count $<100 \times 10^9$/L; received heparin treatment within 48 hours with an activated partial thromboplastin time (APTT) ⩾ 35s;currently taking oral warfarin with an international normalized ratio (INR)>3;Note:Patients without a history of coagulation abnormalities or suspicion of coagulation abnormalities do not need to wait for laboratory test results before enrollment;

7) Seizures at stroke onset or during the course, hard to making accurate baseline NIHSS score;

8) Female who is known to be pregnant or lactating at time of admission;

9) Current participation in another investigational drug study or medical device treatments that may interfere with the results of this study;

10) Other conditions deemed unsuitable for participation by the investigator or that may pose significant risks to the patient.

3.2.2. Imaging Exclusion Criteria

1) Evidence of intracranial hemorrhage on CT/MRI, including cerebral parenchymal hemorrhage,intraventricular hemorrhage, subarachnoid hemorrhage,and subdural/extradural hemorrhage;

2) Significant mass effect with midline shift as confirmed on CT/MRI;

3) Aortic dissection;

4) Multiple intracranial large vessel occlusions confirmed by CTA or MRA, with an inability to clearly identify the vessel responsible for symptoms, such as bilateral middle cerebral artery occlusions or occlusions involving both the middle cerebral artery and basilar artery;

5) Suspected or confirmed occluded artery consist the symptom is non-acute occlusion.l.

4. Intervention

For subjects who have provided informed consent and meet the inclusion/exclusion criteria, the study site will utilize a central randomization system to allocate them in a 1:1 ratio between the intervention group and the control group.

EVT+BMM group (Intervention Group): patients assigned into the intervention group will immediately receive EVT+BMM according to the local guidelines. Interventionists will select the

optimal EVT strategy and device based on the patient's condition, including stent-retriever thrombectomy, aspiration thrombectomy, intra-arterial thrombolysis, balloon angioplasty, stent implantation or a combination of these therapies. BMM was performed according to the identical protocol used in the control arm.

BMM group (Control Group): patients assigned into the control group will receive the BMM alone according to local guidelines, including antiplatelet agents, anticoagulants, thrombolysis, etc., but without any EVT. In the control group, rescue EVT is permitted if neurological deterioration produces a NIHSS increase ⩾4 points and the patients fulfil current EVT guidelines (NIHSS ⩾6 and onset-to-treatment time⩽24 hours). Rescue EVT follows the same procedural protocol as that employed in the intervention arm.

5. Randomization and Blinding

5.1.1. Randomization

Participants were randomized 1:1 into the EVT + BMM group (intervention group) and BMM alone group (control group) with a central internet-based system. Central block randomization will be employed, stratified by:

1. Study sites；
2. Occlusion locations (Intracranial ICA; MCA M1; MCA M2).

The randomization sequence was generated by an independent trial statistician and remained concealed until assignment. Subjects in the screening phase may be excluded from randomization for various reasons. Once a screened subject is excluded during the randomization phase, completion of protocol-specified follow-up will no longer be required.

5.1.2. Blinding

To ensure objective and accurate study results, this study has established independent third-party adjudication and evaluation bodies for various efficacy and safety endpoints to perform blinded independent assessments, effectively controlling bias in the study results.

1. The 90-day post-randomization mRS score, EQ-5D-5L scale score, and 90-day post-randomization Barthel Index will be evaluated by blinded site investigators unaware of subject’s group allocation.

2. An independent third-party core laboratory will be established to independently review and

interpret collected imaging records from subjects at baseline, intraoperative, and postoperative follow-up visits, all while blinded to the subjects' group allocations. This will assess subjects' vascular occlusion and perfusion status, intraoperative revascularization outcomes, postoperative bleeding conditions, and other relevant parameters.

3. An Outcome Assessment Committee(OAC) will be established to independently adjudicate the 90-day post-randomization mRS score in a blinded manner.

4. A Clinical Events Committee(CEC) will be established to independently adjudicate in a blinded manner whether serious adverse events related to endovascular therapy occurred during the procedure, whether intracranial hemorrhage is symptomatic, and all SAEs and AEs of special interest.

6. Outcome Measures and Assessment Methods

6.1. Efficacy Evaluation

Primary Efficacy Endpoint:

Proportion of mRS scores 0 or 1 assessed at 90±7 days after randomization, defined as an excellent functional outcome.

Secondary Efficacy Endpoints:

1) Change in NIHSS at 7±1 days or discharge;

2) Distribution of mRS scores at 90±7 days (shift analysis);

3) Favorable neurological function prognosis (mRS 0-2) at 90±7 days;

4) EQ-5D-5L score at 90±7 days;

5) Barthel Index score of 95-100 at 90±7 days.

6.2. Safety Evaluation

Secondary Safety Endpoints:

1) Symptomatic intracranial hemorrhage (sICH) within 48 hours (Heidelberg criteria);

2) END within 7 days (defined as an increase in NIHSS score ≥4 or ≥2 in one item);

3) All-cause mortality at 90±7 days;

4) Any type of ICH post-randomization (Heidelberg criteria);

5) Rescue EVT rate in the control group;

6) Procedure -related complication: vessel perforation, vessel dissection, vasospasm, access-site hematoma, etc.

7. Sample Size Determination

MILD-MT trial is designed as a multicenter randomized controlled superiority study, which will be performed using a block randomization method. The primary outcome is the proportion of subjects with excellent outcome (mRS 0-1) at 90 days. Based on EXTEND-IA[1]analysis of mild stroke with large vessel occlusion, when perfusion mismatch exists, the proportion with mRS 0-1 was 51.2% in control group and 65.7% in the intervention group. Given that this study design requires a perfusion mismatch volume ≥50 ml, the expected proportion for the intervention group is 67.5% and for the control group is 51.0%.

Assuming a two-sided type I error (α) of 0.05, power (1-β) of 0.8, and a 1:1 allocation ratio, with one planned interim analysis after 50% of subjects have completed 90-day follow-up, using the O'Brien-Fleming alpha spending function to ensure the overall two-sided type I error does not exceed 0.05. Calculation using PASS 2023 yields a sample size of 135 per group. Accounting for a 10% loss to follow-up, the final enrollment target was set at 150 per group, totaling 300 participants.

An interim analysis is planned when 50% of randomized subjects (n=150) have completed the 90-day follow-up. The O’Brien–Fleming spending function will be used to control the overall two-sided type I error at 0.05. Approximately 0.003 of the α will be spent at the interim analysis, leaving approximately 0.048 for the final analysis.

8. Analysis Sets

Intention-to-Treat (ITT) Population: The ITT population is defined as the analysis set consisting of all randomized patients, regardless of whether they received the assigned intervention, and all such patients are included in this analysis population. This population will serve as the basis for evaluating efficacy and safety.

Per-Protocol Set (PPS): The PP set will include subjects from the efficacy analysis who did not have relevant protocol deviations. This includes subjects who met all inclusion criteria and none of the exclusion criteria, received the corresponding standard treatment per protocol, and have data for the primary efficacy endpoint. PP analysis will primarily be used for sensitivity analysis.

PPS must meet the following:

1. Met all study inclusion criteria and none of the exclusion criteria;

2. Following randomization, treatment will be administered according to the study protocol: subjects assigned to the intervention Group will promptly undergo endovascular therapy, while

subjects assigned to the control group will receive best medical treatment;

3. In the intervention Group, if angiography via artery puncture revealed spontaneous recanalization of the originally occluded vessel and no endovascular intervention was performed;

4. In the control group, if neurological deterioration (NIHSS increase ≥4, total score >6) occurred within 24 hours of onset and rescue endovascular therapy was performed.

9. Statistical Analysis Methods

9.1. General Principles

9.1.1. Basic Statistical Methods

Statistical Description: For quantitative variables, mean, standard deviation, median, minimum, maximum, lower quartile (Q1), and upper quartile (Q3) will be calculated. For categorical variables, counts and percentages will be presented.

Statistical Inference: For between-group comparisons of baseline characteristics, quantitative variables will be compared using two-sample t-test (if assumptions of normality and homogeneity of variance hold) or Wilcoxon rank-sum test. Categorical variables will be compared using Chi-square test or Fisher's exact test (if Chi-square test is not applicable). Ordinal variables will be compared using Wilcoxon rank-sum test or CMH test.

9.1.2. Significance Level

This study includes one formal interim analysis, to be conducted when 50% (150 subjects) have completed 90-day follow-up post-randomization. The O'Brien-Fleming alpha spending function will be used to ensure the overall two-sided type I error does not exceed 0.05. The interim analysis will consume approximately α=0.003 (two-sided), and the final analysis will use approximately α=0.048 (two-sided). If the trial is terminated early, the significance threshold will be adjusted accordingly to reflect the spent α.

The final analysis for the primary outcome, including possible sensitivity analyses, will be conducted using a two-sided significance level of 4.8%.

For analyses of any other secondary efficacy or safety endpoints, no multiplicity adjustment will be performed.

9.1.3. Statistical Software

Statistical analysis will be performed using SAS 9.4 software.

9.2. Subject Enrollment and Completion Distribution

Based on all populations, the number of screened, randomized, treated, and completed subjects will be summarized. The sizes of different analysis sets per group will be summarized. A CONSORT flowchart will be utilized to illustrate the research flow, distribution of participants from screening to final analysis, along with corresponding reasons.

9.3. Demographics and Baseline Analysis

Demographic characteristics (age, gender, personal history, height, BMI, etc.), medical history, drug allergy history, past and current medical history will be summarized by treatment groups. Quantitative variables like age, height, BMI will be compared between groups using t-test/Wilcoxon rank-sum test. Categorical variables like gender, past history, allergy history will be compared using Chi-square test/Fisher's exact test. Ordinal variables like symptom severity will be compared using CMH Chi-square test or Wilcoxon rank-sum test.

9.4. Overview of Endovascular and Medical Treatments

Interventions received during the study will be described by intervention group. Details of best medical therapy (including type of anticoagulant, antiplatelet, thrombolytic, etc.) in both groups will be summarized. For the intervention Group, details of endovascular therapy will be summarized, including thrombectomy first line, eTICI grade after endovascular therapy, use of distal access catheter, etc.

9.5. Efficacy Analysis

Efficacy analysis will be performed on both the ITT and PPS.

9.5.1. Primary Efficacy Endpoint Analysis

- Primary Analysis

The number and percentage of subjects achieving excellent neurological outcome (mRS 0-1) at 90 ± 7 days post-randomization will be summarized by intervention group. A comparison of the excellent neurological outcome rates between the experimental and control groups will be performed at a significance level of $\alpha = 0.048$ (two-sided) and $\beta = 0.2$. The Cochran-Mantel-Haenszel (CMH) chi-square test will be used for the between-group comparison. The 95% confidence interval for the rate difference between the two groups will be calculated using the Mantel-Haenszel method, with adjustment for key prognostic factors in the analysis.

Dichotomous analysis will be performed for the mRS at 90±7 days post-randomization, whereby the scale is categorized into a binary outcome of "Excellent Outcome" (score 0-1) or "Non-Excellent Outcome" (score 2-6). This analysis will be conducted using an unadjusted random-effects logistic regression model with a binomial outcome and a logit link function. The intervention effect will be presented as the odds ratio (OR) for achieving an excellent outcome, along with its 95% confidence interval.

- Adjusted Analysis

Adjusted analysis will be performed by adding the following covariates to the primary random-effects logistic regression model: recruitment center, age (as a continuous variable), occlusion location (intracranial segment of the internal carotid artery; M1 segment of the middle cerebral artery; M2 segment of the middle cerebral artery). The adjusted treatment effect will be reported as an adjusted odds ratio (OR) along with its 95% confidence interval (CI).

For centers with an insufficient number of subjects, adjacent centers with similar geographic locations will be combined according to the principle of geographical proximity to ensure adequate sample size for the adjustment of center effect. Only small centers with a small sample size (n≤5) will be merged.

- Subgroup Analysis
  - ✓ Age (≤65 years vs. >65 years)
  - ✓ Gender (Male and Female)
  - ✓ NIHSS before randomization (0-3 points and >3 points)
  - ✓ Time from onset to randomization(≤6 hours and >6 hours)
  - ✓ Intravenous thrombolysis(Yes vs. No)
  - ✓ Cause of stroke (Large artery atherosclerosis, Cardioembolic and Others)
  - ✓ Occlusion site (intracranial segment of ICA, M1 segment of the middle cerebral artery, M2 segment of the middle cerebral artery).
  - ✓ Imaging perfusion mismatch volume (≤70 ml and >70 ml)

Analyses for each subgroup will be performed by adding the subgroup variable and its interaction with intervention as fixed effects to the primary logistic regression model. Within each subgroup, summary measures will include raw counts and percentages for each treatment group, and the treatment effect OR and its 95% CI. Results will be presented in a forest plot, along with the P-value for heterogeneity corresponding to the interaction term between intervention and the subgroup variable.

- Handling of Missing Data

The primary efficacy endpoint is the number of subjects achieving excellent neurological outcome (mRS 0-1 point) at 90±7 days post-randomization. Considering some subjects may be lost to follow-up due to death or severe deterioration after discharge, all missing 90-day mRS scores will be imputed with the worst possible score (i.e., impute score 6 for subjects with unknown vital status, and score 5 for known survivors with missing mRS score). The analysis will therefore be performed after imputing all missing data under the assumption of poor neurological outcome.

- PP Population Analysis

All secondary outcome analyses described in this section will be performed in the efficacy (primary) analysis set and the PP (sensitivity) analysis set defined in Section 3.2..

9.5.2. Secondary Efficacy Endpoint Analysis

(1) Proportion of subjects with favorable neurological outcome (mRS 0-2 points) at 90±7 days post-randomization

The number and percentage of subjects with favorable neurological outcome (mRS 0-2) at 90±7 days will be summarized by intervention group. Dichotomous analysis of mRS will be performed using the same logistic regression model as in section 9.5.1, categorizing mRS as "favorable outcome" (score 0-2) or "non-favorable outcome" (score 3-6). The covariate adjustment method described in section 9.5.1 will also be applied, but no subgroup analysis or imputation analysis is planned for this outcome.

(2) Distribution of mRS scores (mRS shift) at 90±7 days post-randomization

The distribution of mRS scores at 90±7 days post-randomization will be analyzed using ordinal logistic regression, with treatment group as a fixed effect and center as a random effect, using baseline mRS score as an ordinal outcome. The intervention effect will be expressed as the OR for a better outcome (i.e., lower mRS score) and its 95% CI, with the control group as reference (OR >1 indicates a lower mRS score in the intervention group compared to the control group).

(3) Change in NIHSS score at 7±1 days post-randomization or at discharge

For quantitative measures, summary statistics including mean, standard deviation, median, minimum, maximum, first quartile (Q1), and third quartile (Q3) will be calculated for NIHSS scores at baseline and at 7±1 days post-randomization or discharge, as well as for the change from baseline. Between-group comparisons for each assessment will be performed using t-tests or Wilcoxon rank-sum tests. Furthermore, analysis of covariance (ANCOVA) will be conducted with the change from baseline in the NIHSS score as the dependent variable, treatment group as a fixed effect, center as a

random effect, and baseline NIHSS score as a fixed covariate. The least squares mean (LSmean), difference in LSmeans, and corresponding 95% confidence interval will be estimated for the intervention Group versus the control group. No subgroup or imputation analyses are planned for this outcome.

(4) EQ-5D-5L score at 90±7 days post-randomization

For the quantitative assessment, summary statistics including mean, standard deviation, median, minimum, maximum, first quartile (Q1), and third quartile (Q3) will be calculated for the EQ-5D-5L scores at 90±7 days post-randomization. Between-group comparisons for these evaluation metrics will be performed using t-tests or Wilcoxon rank-sum tests. Meanwhile, an analysis of covariance will be conducted with the EQ-5D-5L score at 90±7 days post-randomization as the dependent variable, treatment intervention as a fixed effect, and center as a random effect. This analysis will estimate the least squares means (LS means), the difference in LS means between the experimental and control groups, and the corresponding 95% confidence interval. No subgroup or imputation analyses are planned for this outcome.

(5) Proportion of subjects with Barthel Index score of 95-100 at 90±7 days post-randomization

The number and percentage of subjects with a Barthel Index score of 95 or 100 at 90±7 days will be summarized by intervention group. Dichotomous analysis of the Barthel Index will be performed using the same logistic regression model as in section 9.5.1, categorizing it as "Criteria met" or "Criteria not met". As a quantitative variable, the Barthel Index score at 90±7 days will be summarized (mean, SD, median, min, max, Q1, Q3), and between-group comparisons will be made using t-test or Wilcoxon rank-sum test. No subgroup or imputation analysis is planned for this outcome.

9.6. **Safety Analysis**

9.6.1. Safety Endpoint Event Analysis

Safety endpoint events including symptomatic intracranial hemorrhage within 48 hours post-randomization, any intracranial hemorrhage post-randomization (per Heidelberg criteria), early neurological deterioration within 7 days post-randomization, all-cause death within 90±7 days post-randomization, and any serious adverse event will be reported as the number and proportion of subjects experiencing the event. The intervention effect will be estimated using the same method as for the dichotomous mRS analysis, applying the covariate adjustment described in section 9.5.1; however, no subgroup or imputation analysis is planned for these outcomes.

9.6.2. Endovascular Treatment-related Complication Analysis

For subjects who underwent endovascular treatment, the number and proportion of subjects reporting various types of endovascular treatment-related complications will be described separately. These include vessel perforation, vessel rupture, vasospasm requiring treatment, arterial dissection, puncture site hematoma/pseudoaneurysm, embolism to a new territory, subarachnoid hemorrhage, etc.

9.7. **Interim Analysis**

9.7.1. Data and Safety Monitoring Board(DSMB)

To enhance the safety of the intervention, the trial will be overseen by an independent Data and Safety Monitoring Board (DSMB). The DSMB will dynamically assess the risks and benefits of the two therapies by monitoring efficacy and safety data, and will provide recommendations to the Steering Committee on whether to continue or terminate the study. The DSMB operates independently according to its charter. Members assess trial baseline data, safety, and efficacy endpoints in an unblinded manner. The first DSMB meeting will be held before the first subject is enrolled. After enrollment begins, meetings will be held every 6 months, and one formal interim analysis will be conducted during the study.

9.7.2. Planned Interim Analysis

This study plans to conduct one interim analysis when 90-day follow-up is completed for 50% (150 subjects) of the randomized subjects. The O'Brien-Fleming spending function will be used to ensure that the overall type I error rate does not exceed a two-sided 0.05. The interim analysis will consume approximately α=0.003 (two-sided), leaving approximately α=0.048 (two-sided) for the final analysis.

The interim analysis will be performed by an independent Data and Safety Monitoring Board (DSMB), which is composed of third-party members with expertise in medicine, statistics, and other relevant fields.

10. **Reference**

[1] Sarraj A, Albers GW, Blasco J, et al. Thrombectomy versus Medical Management in Mild Strokes due to Large Vessel Occlusion: Exploratory Analysis from the EXTEND-IA Trials and a Pooled International Cohort. Ann Neurol. 2022;92(3):364-378.

11. Appendix

Appendix 1 Modified Rankin Scale

Patient's Condition	Score
No symptoms at all	0
No significant disability despite symptoms; able to carry out all usual duties and activities.	1
Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.	2
Moderate disability; requires some help but able to walk without assistance.	3
Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.	4
Severe disability; bedridden, incontinent, and requires constant nursing care and attention.	5
Death	6

Assessment Method for the Modified Rankin Scale

The Modified Rankin Scale is used to measure functional recovery in patients after a stroke. The text in bold presents the formal definition for each grade. Text in italics provides further guidance aimed at reducing potential variability among different raters, but does not prescribe a specific interview structure. Please consider only symptoms that have occurred since the stroke. If a patient can walk without assistance from another person, albeit with the aid of a device, they are considered able to walk independently. If two grades seem equally applicable to the patient, and further questioning is unlikely to yield a definitively correct choice, the more severe grade should be selected.

0-No symptoms

No new functional limitations or symptoms are perceived by the patient since the stroke, although minor symptoms may be present.

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

The patient has some symptoms resulting from the stroke (whether physical or cognitive, e.g., affecting speech, reading, writing, bodily movement, sensation, vision, swallowing, or emotion) but can continue to perform all work, social, and recreational activities engaged in prior to the stroke. A key question to distinguish between Grade 1 and Grade 2 (see below) could be: "Is there anything you used to do regularly before the stroke that you can no longer do?" Activities occurring more than once a month are considered "usual".

2-Slight disability; unable to perform all previous activities but able to manage own affairs without assistance

The patient is no longer able to perform certain activities that were possible before the stroke (e.g., driving, dancing, reading, or working) but can manage daily self-care without help from others. The patient can dress, walk, eat, use the toilet, prepare simple meals, shop, travel locally, etc., without assistance. The patient does not require supervision. It is envisaged that a patient at this level could stay at home alone for a week or longer without care.

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

At this grade, the patient can walk independently (may use a walking aid) and can dress, use the toilet, eat, etc., independently, but requires assistance for more complex tasks. For example, someone else may need to take over shopping, cooking, or cleaning, and may need to visit the patient more than once a week to ensure these activities are completed. The assistance required relates not only to physical care but often to advice; for instance, patients at this level will 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 requires help from others for daily living activities, whether for walking, dressing, using the toilet, or eating. The patient needs to be looked after at least once, and usually twice or more per day, or must live very close to a caregiver. To distinguish between Grade 4 and Grade 5 (see below), consider whether the patient can routinely be left alone for reasonable periods during the day.

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

Requires care throughout the day and night, several times, although not necessarily from a trained nurse.

6 -Patient death

Appendix 2. National Institutes of Health Stroke Scale (NIHSS)

Note that record the actual time of each NIHSS assessment. Score according to the form and record the results. Do not change the scores; the scores should reflect the patient's actual condition, not what the doctor thinks the patient's condition should be. Check quickly and record results simultaneously. Do not coach the patient unless necessary (e.g., repeatedly asking the patient to make a certain effort). If some items are not assessed, explain in detail in the form..

	Examination	**Score**
1a	**Level of Consciousness:** Even if a full evaluation is not possible (e.g., due to intubation, language barrier, tracheal trauma, bandages, etc.), the examiner must choose 1 response. Score 3 only if the patient does not respond to a noxious stimulus (not a reflex).	0 = Alert; keenly responsive 1 = Drowsy; but can be aroused with minor stimulation to obey, answer, or respond 2 = Stuporous or obtunded; requires strong or repeated stimulation to make non-stereotyped movements 3 = Comatose; responds only with reflex motor or autonomic effects, or is totally unresponsive, flaccid, and areflexic
1b	**LOC Questions:** (Score only the initial answer, do not prompt.) Ask the patient the month and their age. The answers must be correct—approximations are not acceptable. A score of 2 is given if the patient has aphasia or is stuporous/coma and cannot comprehend the questions. A score of 1 is given if the patient cannot speak due to endotracheal intubation, orotracheal trauma, severe dysarthria, language barrier, or any other reason not attributable to aphasia.	0 = Answers both correctly. 1 = Answers one correctly. 2 = Answers neither correctly.

1c	**LOC Commands:** Ask the patient to open and close eyes, then to grip and release the non-paretic hand. If the hands cannot be tested, use another command (stick out tongue). Score only the initial attempt. Give credit if an unequivocal attempt is made but not completed due to weakness. If no response to command, demonstrate the action, then score. For patients with trauma, amputation, or other physical impairments, give an appropriate command.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2	**Gaze:** Test only horizontal eye movements. Score for voluntary or reflexive (doll's eye) eye movement. If the eye can be corrected by voluntary or reflexive movement, score 1 point. If there is isolated peripheral nerve palsy (Ⅲ, Ⅳ, Ⅵ), score 1 point. Gaze can be tested in aphasic patients. For patients with eye trauma, eye dressings, blindness, or visual field defects, the examiner selects a reflexive movement to test: establish contact with the eye, then move from one side to the other—gaze palsy can occasionally be detected.	0 = Normal. 1 = Partial gaze palsy (abnormal gaze in one or both eyes, but no forced gaze or total gaze palsy). 2 = Forced gaze deviation or total gaze palsy (cannot be overcome by oculocephalic maneuver).
3	**Visual Fields:** Test upper and lower quadrants by finger counting or visual threat. If patient can see the fingers laterally, score normal. If monocular or eye enucleated, test the other eye. Score 1 for definite but not total asymmetry (including quadrantanopia). Score 3 for bilateral total blindness (any cause), including cortical blindness. Score 1 for patients who are near death (result is used to answer question 11).	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (including cortical blindness).

4	**Facial Palsy:** Ask the patient to show teeth, raise eyebrows, and close eyes via verbal command or gesture. For poorly responsive or non-comprehending patients, score symmetry of grimace in response to noxious stimuli. If facial trauma/bandages, orotracheal tube, tape, or other physical barriers obscure the face, move these to the extent possible for assessment.	0 = Normal. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5	**Upper Limb Movement:** Arm extension: Place arms at 90° (if sitting) or 45° (if supine). Ask to hold for 10 seconds; for aphasic patients, use verbal or gesture encouragement, not noxious stimuli. The examiner may lift the patient's arm to the required position, encouraging the patient to hold. Score only the affected side.	0 = No drift; limb holds 90° (or 45°) for full 10 seconds. 1 = Drift; limb holds 90° (or 45°) but drifts down before full 10 seconds; does not hit bed or other support. 2 = Can resist some gravity, but cannot reach/maintain seated 90° shoulder abduction or 45° elbow flexion; drops quickly. 3 = No effort against gravity; limb falls immediately. 4 = No movement. 9 = Amputation or joint fusion; explain: _____
6	**Lower Limb Movement:** Leg flexion: Place leg at 30°. Hold for 5 seconds; for aphasic patients, use verbal or gesture encouragement, not noxious stimuli. The examiner may lift the patient's leg to the required position, encouraging the patient to hold. Score only the affected side.	0 = Maintains the required position for 5 seconds without dropping 1 = Drops before 5 seconds, but does not hit the bed 2 = Drops onto the bed within 5 seconds, but can resist gravity 3 = Drops rapidly; cannot resist gravity 4 = No movement 9 = Amputation or joint fusion; explain: _____

7	**Ataxia：** Aim is to detect signs of bilateral cerebellar lesions. Test with eyes open. If visual field defect, ensure testing is in intact field. Test finger-nose and heel-shin bilaterally. Score only if ataxia is disproportionate to weakness. If patient cannot understand or limb is paralyzed, score 0. For blind patients, test touching nose with outstretched arm. If amputation or joint fusion, score 9 and explain clearly.	0 = No ataxia 1 = Ataxia in one limb 2 = Ataxia in two or more limbs
8	**Sensory:** Test with pinprick. When testing, observe sensation and grimace in stuporous or aphasic patients by pricking and withdrawing the stimulus. Score only sensory loss related to stroke. For hemisensory loss, test multiple body areas accurately: arm (not hand), leg, trunk, face. Score 2 for severe or total sensory loss. Score 1 or 0 for stuporous or aphasic patients. Score 2 for brainstem stroke with bilateral sensory loss. Score 2 for unresponsive and quadriplegic patients. Score 2 for coma patients (1a=3).	0 = Normal; no sensory deficit 1 = Mild to moderate; reduced sharpness (dull) of pinprick sensation on the affected side, or only tactile sensation present
9	**Speaking:** Test naming, reading. Ask patient to name items and read from a list of sentences. Judge comprehension from patient's response and response to commands during general neurological exam. If visual deficit interferes, have patient identify objects placed in hand, repeat, and produce speech. For intubated patients, have them write answers. Score 3 for coma patients (1a=3). Choose a score for confused or uncooperative patients, but score 3	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia: some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. 2 = Severe aphasia: communication is through fragmentary expression; listener must infer, ask, guess; range of information exchanged is limited. 3 = Mute, global aphasia: no usable speech or comprehension.

	only for mute or patients who follow no commands.	
10	**Dysarthria:** Do not tell patient why you are testing. Read or have patient repeat words from the attached list. If patient has severe aphasia, assess clarity of articulation of spontaneous speech. Score 9 for intubated or other physical barriers preventing speech, and note the explanation.	0 = Normal. 1 = Mild-to-moderate dysarthria, patient slurs at least some words, but can be understood. 2 = Patient's words are slurred and cannot be comprehended 9 = Intubated or other physical barrier; explain: _____
11	Neglect syndrome： If the patient has severe visual loss that precludes bilateral simultaneous visual testing, but skin sensation is intact, the score should be normal. If the patient is aphasic but demonstrates clear attention to both sides, the score should be normal. Neglect is assessed by testing the patient's ability to recognize simultaneous skin sensation and visual stimuli on both the left and right sides. Present the standard picture to the patient and ask them to describe it. The examiner encourages the patient to look carefully and identify features on both sides of the picture. If the patient fails to identify parts of one side of the picture, this is considered abnormal. Next, the examiner asks the patient to close their eyes and checks bilateral skin sensation by testing pinprick sensation on the upper and lower limbs separately. If the patient shows neglect on one side, this is considered abnormal.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

Appendix 3. EuroQol 5-Dimension 5-Level Scale（EQ-5D-5L）

Item	Score
Mobility	□I have no problem walking around —— 1 point □I have slight problems walking around——2 points □I have moderate problems walking around——3 points □I have severe problems walking around ——4 points □I am unable to walk around——5 points
Self-care	□I have no problems washing or dressing myself ——1 Point □I have slight problems washing or dressing myself ——2 Points □I have moderate problems washing or dressing myself ——3 Points □I have severe problems washing or dressing myself ——4 Points □I am unable to wash or dress myself ——5 Points
Usual activities	□I have no problems doing my usual activities ——1 Point □I have slight problems doing my usual activities ——2 Points □I have moderate problems doing my usual activities ——3 Points □I have severe problems doing my usual activities ——4 Points □I am unable to do my usual activities ——5 Points
Pain/Discomfort	□I have no pain or discomfort ——1 Point □I have slight pain or discomfort ——2 Points □I have moderate pain or discomfort ——3 Points □I have severe pain or discomfort ——4 Points □I have extreme pain or discomfort ——5 Points
Anxiety/Depression	□I am not anxious or depressed ——1 Point □I am slightly anxious or depressed——2 Points □I am moderately anxious or depressed——3 Points □I am severely anxious or depressed——4 Points □I am extremely anxious or depressed——5 Points

Appendix 4. Barthel Index

Item	Score	Content
I. Feeding	**10**	Can independently pick up food in front with chopsticks at a reasonable pace (approx. one bite every 10 seconds). If assistive devices are needed, can put them on and take them off without help.
	5	Needs partial assistance (e.g., cutting bread, spreading butter, picking up dishes, serving rice).
	0	Fully dependent on others.
II. Transfer	**15**	Independent.
	10	Needs minimal assistance (from 1 person) or verbal guidance.
	5	Needs assistance from 2 people or 1 physically strong and skilled person.
	0	Fully dependent on others.
III. Grooming	**5**	Can independently wash face, hands, brush teeth and comb hair.
	0	Needs assistance from others.
IV. Toileting	**10**	Can independently enter and exit the toilet without soiling clothes, and dress properly afterward. For those using a bedpan, can clean the bedpan independently.
	5	Needs assistance to maintain balance, adjust clothes or use toilet paper. For those using a bedpan, can place and retrieve the bedpan independently but relies on others for cleaning.
	0	Needs full assistance from others.
V. Bathing	**5**	Can bathe independently (either tub bath or shower).
	0	Needs assistance from others.
VI. Ambulation (45m on flat ground)	**15**	Can walk independently for more than 50 meters, with or without assistive devices.
	10	Needs slight physical support or verbal guidance to walk for more than 50 meters.
	5	Unable to walk, but can independently operate a wheelchair (including turning, passing through doors, and approaching tables/beds) and propel it for more than 50 meters.
	0	Needs assistance from others.
VII. Stair Climbing & Descending	**10**	Can climb up and down stairs independently (holding handrails or using walking sticks is allowed).

	5	Needs slight assistance or verbal guidance.
	0	Unable to climb stairs.
VIII. Dressing & Undressing	**10**	Can independently put on and take off clothes, shoes and assistive devices.
	5	Can complete more than half of the process independently with assistance from others.
	0	Needs assistance from others.
IX. Bowel Control	**10**	Can be controlled.
	5	Occasional incontinence (less than once a week).
	0	Incontinent or comatose.
X. Bladder Control	**10**	Can be controlled.
	5	Occasional incontinence (less than once a week), or urinary urgency (unable to wait for a bedpan or reach the toilet in time), or needs assistance with bladder care.
	0	Incontinent, comatose, or requires catheterization by others.
Total Score		

Appendix 5. Heidelberg Bleeding Classification

According to the Heidelberg criteria formulated at the 12th International Stroke Thrombectomy Workshop held in Germany in 2015, symptomatic intracranial hemorrhage is defined as (meeting all of the following conditions):

1. Any form of intracranial hemorrhage (including Heidelberg grades 1a, 1b, 1c, 2, 3a, 3b, 3c, 3d) detected by imaging (head CT or MRI) within 48 hours after endovascular therapy, confirmed by a radiologist;

2. Clinical deterioration found in the patient: NIHSS score increases by ⩾4 points compared to the last score before deterioration, or any single NIHSS item increases by ⩾2 points, or leads to intubation, decompressive craniectomy, ventricular drainage, or other major medical/surgical intervention;

3. No other cause besides intracranial hemorrhage can explain the clinical deterioration.

Heidelberg Classification	
Grade/Type	**Grade/Type**
Hemorrhage in infarcted brain tissue without significant mass effect (Grade 1)	□
Scattered small hemorrhagic spots without mass effect (Grade 1a / Type H1)	□
Fused hemorrhagic spots into patches without mass effect (Grade 1b / Type H2)	□
Hematoma in infarcted tissue < 30% of the infarct volume, without significant mass effect; intracerebral hemorrhage within or beyond the infarct area (Grade 1c / Type PH1)	□
Hemorrhage in infarcted brain tissue, hematoma volume ≥ 30% of the infarct volume, with obvious mass effect (Grade 2 / Type PH2)	□
Intracerebral hemorrhage outside the infarcted tissue (Grade 3)	□
Hematoma in remote areas from the infarct (Grade 3a)	□

Intraventricular hemorrhage (Grade 3b)	□
Subarachnoid hemorrhage (Grade 3c)	□
Subdural hemorrhage (Grade 3d)	□

Appendix 6. Alberta Stroke Program Early CT Score(ASPECTS)

The Alberta Stroke Program Early CT Score (ASPECTS) is a 10-point quantitative systematic scoring method used to evaluate early ischemic changes on NCCT in patients with acute ischemic stroke in the MCA territory. The MCA territory is divided according to the diagram below. One point is subtracted from the initial score of 10 for each region demonstrating ischemic change. A score of 10 indicates a normal brain CT, and a score of 0 indicates diffuse ischemic involvement throughout the MCA territory. (Yoo AJ, Lancet Neurology).

A: Anterior circulation; P: Posterior circulation.

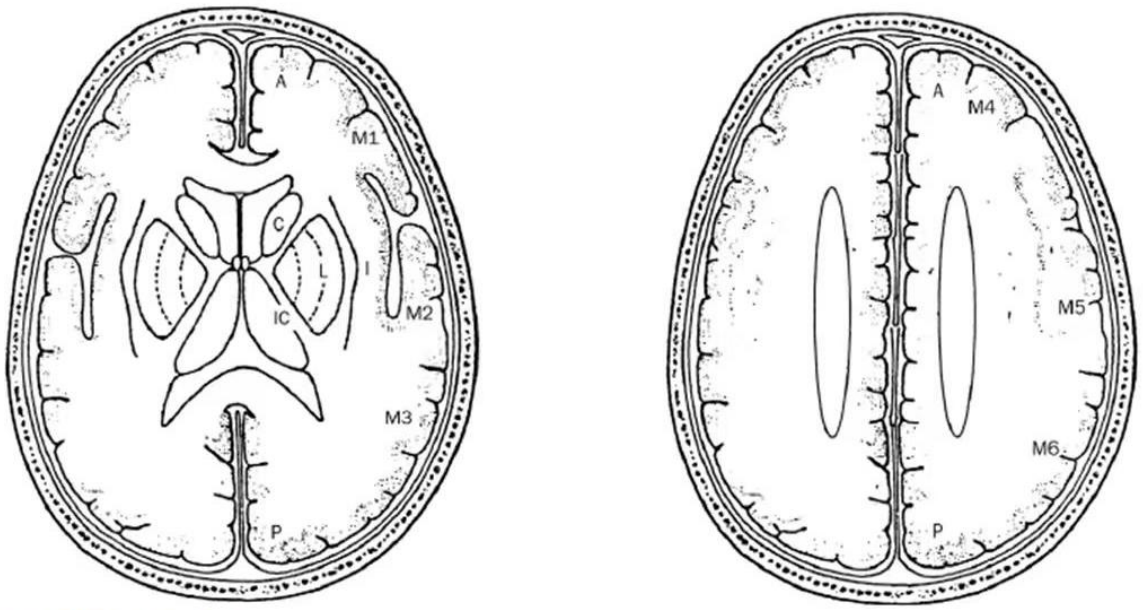


Figure 1: **ASPECTS study form**

10 Regions: C = Caudate; L = Lentiform nucleus; IC = Internal capsule; I = Insular cortex; M1 = Anterior MCA cortex, corresponds to the frontal operculum; M2 = MCA cortex lateral to insula, corresponds to the anterior temporal lobe; M3 = Posterior MCA cortex, corresponds to the posterior temporal lobe; M4 = Anterior MCA territory immediately superior to M1; M5 = Lateral MCA territory immediately superior to M2; M6 = Posterior MCA territory immediately superior to M3.