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Randomised study of bailout intracranial angioplasty following thrombectomy for acute large vessel occlusion (ANGEL-REBOOT): protocol of a multicentre randomised controlled trial

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ABSTRACT

Rationale Unsuccessful thrombectomy of acute large vessel occlusions (LVOs) has been associated with unfavourable outcomes. Multiple randomised controlled trials (RCTs) have reported a failure rate of 12%–41% for thrombectomy procedures. Various factors contribute to failed thrombectomy, including technical difficulties in accessing the occlusion, unsuccessful thrombus retrieval, thrombotic reocclusion and pre-existing intracranial atherosclerotic stenosis. Although some studies have explored balloon dilation or permanent stenting as rescue intracranial angioplasty for failed thrombectomy in individual cases, there is currently no evidence from RCTs on this specific topic.

Aim To evaluate the potential superiority of bailout angioplasty over standard treatment in cases of unsuccessful recanalisation (eTICI 0 to 2a) or residual severe stenosis (>70%) after thrombectomy in acute LVO patients within 24 hours of stroke onset.

Design This study is a multicentre, prospective, randomised, controlled clinical trial designed by investigators. It compares bailout angioplasty with standard therapy and follows an open-label treatment approach while maintaining a blinded outcome assessment (PROBE design). Our objective is to allocate 348 patients in a 1:1 ratio to either receive bailout angioplasty as an intervention or standard therapy as a control, following unsuccessful thrombectomy.

Outcome The main measure of interest is the modified Rankin Scale (mRS) Score, which will be assessed in a blinded manner at 90 (±14) days following randomisation. The primary effect size will be determined using ordered logistic regression to calculate the common OR, representing the shift on the six-category mRS Scale at the 90-day mark. Additionally, the safety outcomes will be evaluated, including symptomatic intracranial haemorrhage within 18–36 hours, severe procedure-related complications and mortality within 90 (±14) days, among others.

Discussion The ANGEL-REBOOT study aims to generate substantial evidence regarding the efficacy and safety of bailout intracranial angioplasty as a treatment option for patients with LVO who have experienced unsuccessful thrombectomy.

Trial registration number NCT05122286.

INTRODUCTION AND RATIONALE

Stroke ranks as the second most prevalent cause of death globally, accounting for approximately 4.4 million fatalities, which represents around 9% of the total annual deaths estimated at 50.5 million. While stroke mortality in Europe and North America has decreased somewhat in recent years,[1] this remains a significant matter in other parts of the world. In China, stroke is still the leading cause of death, resulting in the world's largest stroke burden.[2] The burden of stroke has witnessed a notable increase during the last three decades, particularly in rural China, with stroke incidence and mortality highest in the Northeast (365 and 159/100 000 person-years).

For years, intravenous thrombolysis with recombinant tissue plasminogen activator, commonly known as alteplase, has been considered the sole effective and approved specific treatment for acute ischaemic stroke (AIS). This approach is recommended by international and national guidelines as the standard treatment for AIS. After the first positive clinical trial of thrombolysis in ischaemic stroke, the use of alteplase was limited to treatment initiation within 3 hours of symptom onset. However, based on the findings of the ECASS (Europe Cooperative Acute Stroke Study) III trial, international guidelines have been updated to recommend intravenous thrombolysis for eligible patients up to 4.5 hours from the onset of stroke symptoms.[3–7]

In the context of large vessel occlusions (LVOs), the use of stent-retrievers has led to significant enhancements in recanalisation rates and outcomes when compared with earlier-generation devices. Recent randomised

controlled trials (RCTs), mostly comparing stent-retriever mechanical thrombectomy (MT) with the best medical acute stroke care, demonstrated overwhelming clinical benefit from reperfusion without significantly increased adverse events (AEs).[8] However, even with new-generation devices, MT fails in a relevant proportion of patients (12%–41% in the large RCTs). There are several potential factors that can contribute to failed recanalisation in the context of stroke treatment. These include technical access failure, ineffective thrombus retrieval, thrombotic reocclusion and significant stenosis caused by intracranial atherosclerotic disease (ICAD). The aetiology of LVO varies with ethnicity, with ICAD being much more common in Asia, comprising 33%–37% among all ischaemic strokes.[9 10] Contrarily, in Europe and North America, cardioembolic sources are commonly observed as the leading cause of stroke.[11 12] Typically, cardiac emboli contain a high red blood cell content, which can serve as a predictor for high recanalisation rates after thrombectomy.[13 14] Large artery atherosclerosis is characterised by a significant reduction in the proportion of red blood cells within the affected arteries. This reduction has been found to be decisively associated with lower recanalisation rates.[14] For failed MT cases, intracranial angioplasty with balloon dilatation/stenting is a possible rescue treatment performed for individual cases at experienced centres. Recently, several non-randomised studies have supported bailout intracranial angioplasty with balloon dilatation/stenting for failed MT,[15–23] with a randomised trial as the next logical step.[24]

The ANGEL-REBOOT study aims to address this issue by conducting an RCT focusing on bailout angioplasty with balloon dilatation or stenting in cases of intracranial artery stenosis following failed MT.

METHODS

Design

ANGEL-REBOOT is an investigator-initiated, multicentre, prospective, randomised, controlled, open-label, blinded endpoint study to compare the efficacy and safety of intracranial angioplasty compared with standard treatment in AIS patients up to 24 hours after symptom onset or last known well.

The study flowchart is depicted in figure 1. In the ANGEL-REBOOT study, eligible patients will be randomly assigned to one of two treatment groups: intracranial angioplasty or standard therapy. The study will follow a prospective open-label design, where the assessment of endpoints will be conducted in a blinded manner, ensuring that the treatment assignment remains undisclosed. This trial will be carried out across approximately 40 sites in China.

The ANGEL-REBOOT study employs a group sequential design, which includes preplanned interim analyses at specified time points. The study has predefined stopping rules, enabling the possibility of early termination if a determination of success or futility is reached. This design allows for efficient monitoring of the study's

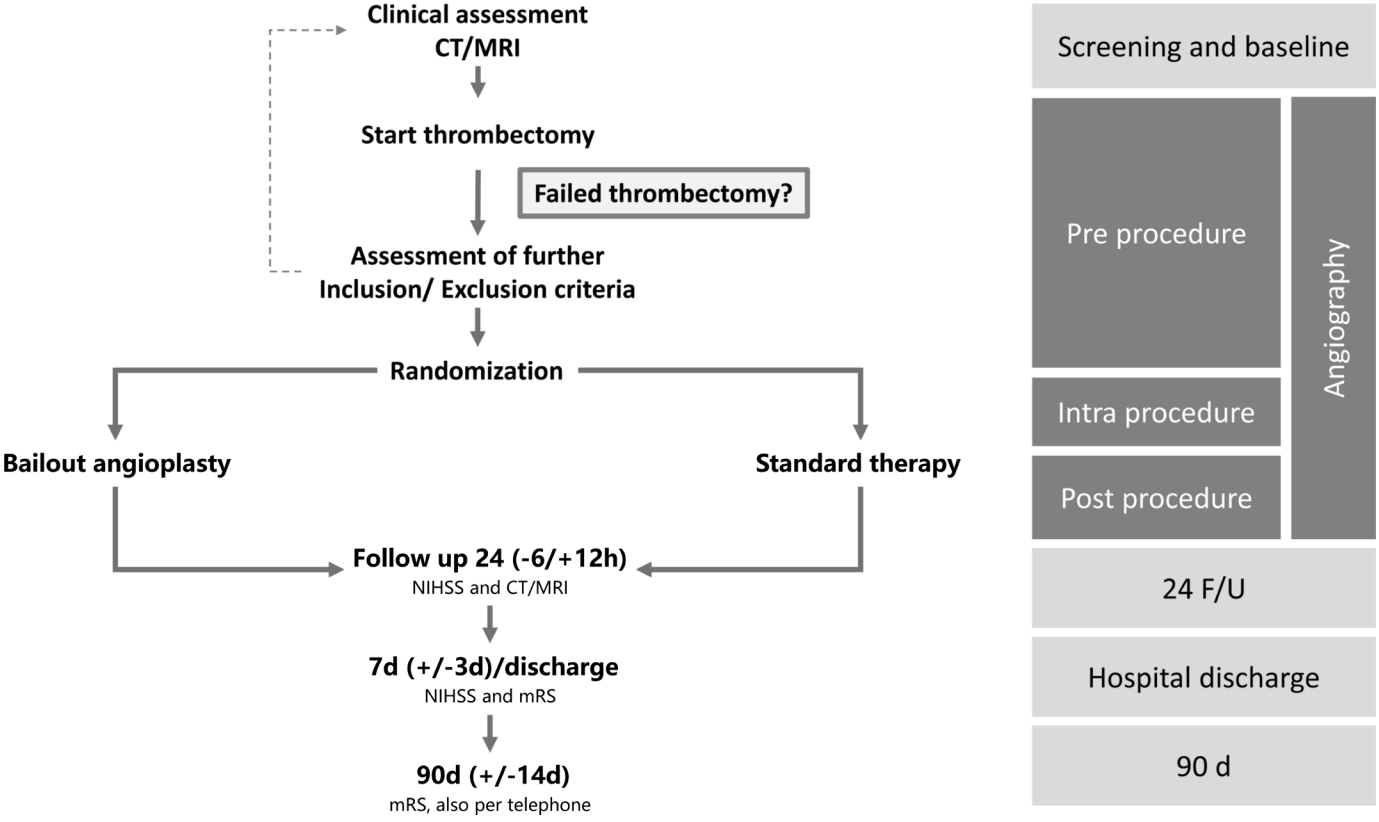

Figure 1 Study flowchart. mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; F/U, follow up.

progress and provides the flexibility to conclude the trial earlier if necessary, based on the predefined criteria.

Patient inclusion and exclusion criteria

Prior to study enrolment and randomisation, candidates must meet all of the following criteria.

Clinical inclusion criteria

1. Age≥18 years.
2. Pre-stroke modified Rankin Scale (mRS) of 0–2.
3. National Institute of Health Stroke Scale (NIHSS) Score ≥6 before randomisation.
4. Time interval from symptom onset to puncture ≤24 hours.
5. Each patient or their legal representative must provide written informed consent before enrolment.

Imaging inclusion criteria

1. For patients with anterior circulation stroke, a CT or DWI-based Alberta Stroke Program Early CT Score (ASPECTS)[25] of ≥6 is required.
2. For patients with posterior circulation stroke, CT or DWI-based posterior circulation ASPECTS (pc-ASPECTS)[26] of ≥6 and Pons-Midbrain Index (PMI)[27] of <3 are required.

Angiographic inclusion criteria

1. AIS resulting from LVO involving the intracranial portion of the internal carotid artery, the M1 segment of the middle cerebral artery, the V4 segment of the vertebral artery and the basilar artery.
2. In cases where recanalisation is not achieved (as indicated by an expanded Thrombolysis In Cerebral Infarction (eTICI)[28] Score of 0–2a) or when there is a presence of significant stenosis (>70%) that remains after 1–3 attempts of thrombectomy using stent-retriever and/or contact aspiration techniques.
3. Previous passage of occlusion with microcatheter obtained.
4. Occluded artery amenable to angioplasty (balloon dilation and/or stenting) by the judgement of the treating neurointerventionalist.

Candidates must not be randomised if any of the following criteria are met:

1. Evidence of intracranial haemorrhage (ICH) on brain imaging before thrombectomy.
2. CT or MRI findings indicating mass effect or the presence of an intracranial tumour.
3. Any indication of intracranial vessel perforation during thrombectomy.
4. Contraindication for antiplatelet treatment.
5. History of contraindication to the use of contrast medium.
6. Current use of oral anticoagulants, such as vitamin K antagonists, with an international normalised ratio greater than 1.7.
7. Current pregnant or breastfeeding status.
8. Known diagnosis of dementia or psychiatric disease that would hinder the ability to complete neurological assessment and follow-up.
9. Life expectancy less than 3 months.
10. Participation in another drug or device trial or anticipated participation within the next 3 months.
11. Any other condition that, in the investigator's judgement, deems the individual unsuitable for enrolment.

Randomisation

Subjects who meet all the inclusion criteria will be enrolled, randomised and assigned a five-digit identification number (subject study number). Then subjects will be randomised to one of the following treatment arms: standard therapy or bailout angioplasty. An adaptive randomisation schedule will be generated using the minimisation method (1:1 ratio) based on stroke severity (NIHSS 6–15 and ≥16), time from symptom onset until arterial puncture (<6 hours and 6–24 hours) and occlusion site (anterior circulation and posterior circulation). To randomise the subjects, an authorised member of the study site staff will access the web-based system with their individual account information and will, at a minimum, input the subject identification number, NIHSS, time from symptom onset and occlusion site. The site will provide a subject treatment assignment. Only one subject may be randomised at a time, and randomisation assignments will be documented.

Blinding

As this is an open-label trial, both the treating physician and the patient will be aware of the treatment allocation. However, to minimise bias, a blinded and trained investigator who is not involved in the treatment will collect 90-day clinical outcomes using standardised forms and procedures. This ensures that the outcome assessment remains unbiased. Members of the Clinical Events Committee (CEC) and the imaging Core-Laboratory (Core-Lab) responsible for reviewing clinical events and imaging data, respectively, will be blinded to the treatment allocation.

Intervention

Thrombectomy before randomisation

In this study, the femoral artery is recommended as the site for arterial puncture. The use of a guiding catheter, long sheath or balloon guiding catheter is also recommended during the procedure. Stent-retriever (Solitaire (Medtronic, USA), Trevo (Stryker, USA), EMBOTRAP (Johnson & Johnson, USA), Captor (HeartCare, China) and other stent-retriever systems) and contact aspiration (Penumbra (Penumbra, USA), Afentta (HeMo, China) and other aspiration systems) are recommended as the first choice for thrombectomy. All thrombectomy devices should be performed in compliance with the intended use and operating instructions, and approved by the National Medical Products Administration of China. Multiple thrombectomy techniques, such as stent-retriever plus aspiration (Solumbra), BAlloon guide with

large bore Distal access catheter with Dual Aspiration with Stent-retriever as Standard approach, double stent-retrievers, etc, are allowed in this study. The treating team has the autonomy to determine the specific approach for thrombectomy in each patient based on their clinical expertise and judgement.

Standard therapy after randomisation (control group)

If a patient is allocated to the standard therapy arm, the decision to continue or terminate the thrombectomy procedure, as well as the consideration of alternative thrombectomy devices or techniques, will be at the discretion of the interventionalist. However, it is important to note that in the standard therapy arm, performing a balloon dilation and/or stenting procedure after randomisation should be avoided as it would be considered a severe protocol violation.

Bailout angioplasty after randomisation (study group)

If a patient is allocated to the bailout angioplasty arm, balloon (Gateway (Stryker, USA), Neuro RX (SinoMed, China), FocuStar (HeMo, China) and other intracranial balloon catheter systems) and stent (Wingspan (Stryker, USA), Apollo (MircoPort, China), Enterprise (Johnson & Johnson, USA), Neuroform EZ (Stryker, USA) and other Intracranial stent systems) approved by the NMPA are recommended as the first choice for angioplasty. The choice between balloon dilation and stenting will be determined by the treating team based on their clinical judgement and expertise. After angioplasty, antiplatelet agents should be used according to the latest guidelines or expert consensus.

Clinical and imaging assessment

Each subject's enrolment in the study is expected to have a duration of 90 days. All study assessments are summarised in table 1. All subjects will be closely monitored and undergo assessments at specific time points: at 24 hours, with a window of −6 to +12 hours from the designated time after randomisation; at 7 days, with a window of +/−3 days from the designated time after randomisation or hospital discharge, whichever comes first; and at 90 days, with a window of +/-14 days from the designated time after randomization. Patients will be evaluated clinically at 24 hours and 7 days by a local trained neurologist. The CEC will assign a final 90-day mRS based on the results of a structured telephone interview by a local trained investigator blinded to the treatment allocation. The Core-Lab will assess imaging to confirm baseline LVO, baseline ASPECTS and pc-ASPECTS/PMI, presence and characterisation of ICH at 24 hours (−6/+12) post randomisation, core infarct volumes and angiographical variables (including final reperfusion status and residual stenosis).

Primary outcome

The primary outcome is the mRS Score at 90 (±14) days after randomisation as an ordinal variable.

Secondary outcomes

The secondary outcomes will be described and compared between the two treatment groups as follows:

1. Rate of good functional outcome (mRS of 0–2) at 90 (±14) days after randomisation.
2. Rate of independent ambulation (mRS of 0–3) at 90 (±14) days after randomisation.
3. EuroQol Five Dimensions (EQ-5D) Score at 90 (±14) days after randomisation.
4. Successfully restoring blood flow (eTICI 2b–3) in the occluded vessel on completion of the procedure is defined as technical success.
5. Core infarct volume at 18–36 hours post randomisation based on FLAIR or T_2-weighted MRI (favoured) or non-enhanced CT, in cases where MRI is not viable.
6. NIHSS Score at 24 hours after randomization.
7. Proportion of target vessel recanalisation (arterial occlusive lesion[29] of 2–3) at 18–36 hours post randomisation, as confirmed by CTA or MRA.

Safety outcomes

All AEs reported will be categorised using the MedDRA coding system based on the System Organ Class and Preferred Term. Tabulations will be conducted using an independent assessment to determine the relationship of the event to the treatment, endovascular procedure and/or disease state. As part of the safety analysis, the following endpoints will be presented for each treatment arm, as applicable:

1. Symptomatic ICH (SICH) defined by the Heidelberg classification[30] within 18–36 hours after randomisation.
2. Serious procedure-associated complications such as dissection and perforation of an intracranial artery, etc.
3. The occurrence of new ischaemic stroke in the downstream territory of the occluded vessel within 90 (±14) days post randomisation.
4. Parenchymal haemorrhage type 2 (PH-2) within 18–36 hours after randomisation.
5. Embolisation in new territories within 18–36 hours post randomisation.
6. Mortality within 90 (±14) days post randomisation.

A blinded Core-Lab imaging assessment will determine ICH, and neurological assessments will be performed at the study site by an independent neurologist certified in the NIHSS, and adjudication of SICH will be done by the CEC.

Data and Safety Monitoring Board (DSMB)

An independent DSMB will convene at regular intervals during the study to review aggregated data and assess the study safety endpoints. The DSMB will apply the predefined protocol definitions to adjudicate the occurrence of clinical study safety endpoints.

The DSMB will review all available aggregated data (eg, AEs), provide counsel to the sponsor on the safety of enrolled and prospective participants, as well as monitor the ongoing validity and scientific integrity of the trial.

Table 1 Summary of study assessments

Study requirements	Screening and baseline	Recanalisation procedure				Follow-up visits	
	Prior to start of study treatment	Preprocedure	Intraprocedure	Immediately postprocedure	24 hours (–6/+12 hours) post-treatment	Hospital discharge or 7 (±3) days	90 (±14) days (76–104 days)
Inclusion/exclusion	X	X					
Informed consent	X						
Clinical assessment, vital signs and physical exam	X	X			X	X	X
Laboratory tests	X						
Subject identification number assignment (assigned at time of ICF)	X						
Randomisation	X						
NIHSS (blinded to treatment)	X				X	X	
mRS (blinded to treatment)	X					X	X
EQ-5D (blinded to treatment)							X
Relevant concomitant medications	X	X	X	X	X	X	X
Treatment medications	X	X	X	X			
Inclusion imaging for ICH and ASPECTS (MRI or CT/CTP as per institutional standard)	X						
eTICI assessment		X	X	X			
Non-enhanced CT or FLAIR/T_2WI post treatment (according to standard of care)					X		
CTA or MRA post treatment (according to standard of care)					X		
Serious adverse events		X	X	X	X	X	X
Protocol deviations		X	X	X	X	X	X
Subject evaluation for study termination		X	X	X	X	X	X

Continued

Table 1 Continued

Study requirements	Screening and baseline	Recanalisation procedure			Follow-up visits	
	Prior to start of study treatment	Preprocedure	Intraprocedure	Immediately postprocedure	24 hours (−6/+12 hours) post-treatment	Hospital discharge or 7 (±3) days	90 (±14) days (76–104 days)

ASPECTS, Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; EQ-5D, EuroQol Five Dimensions Questionnaire; eTICI, expanded Thrombolysis In Cerebral Infarction Score; FLAIR, fluid attenuated inversion recovery; ICF, informed consent form; ICH, intracranial haemorrhage; MRA, magnetic resonance angiography; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; T2WI, T2 weighted imaging.

The DSMB chairperson and committee membership will generate a written charter. This charter will define the criteria for meeting frequency, ongoing safety review, early trial stoppage and site inactivation for excessive protocol deviations. Members of the DSMB will be independent of any affiliation with the sponsor, and they will diligently declare any conflicts of interest that may arise.

Sample size calculation

A formal sample size calculation was based on the primary outcome mRS at 90 (±14) days. Since there is no reliable data for the ordinal mRS distribution in the two groups, the sample size planning was performed for a dichotomised clinical outcome endpoint defined as good (mRS 0–2) versus poor (mRS>2). For the ordinal mRS analysis, we expect a statistical power gain. Based on previous trial data, we expect a good clinical outcome in 25% of the control and 40% of the study groups.

To achieve 80% power in detecting a difference of 15% between two groups, with a two-sided significance level (alpha) of 0.05, using a group-sequential z-test for two independent proportions, a sample size of 156 participants per group (312 participants in total) is required. These findings are contingent on conducting three sequential tests using the O'Brien-Fleming spending function to establish the test boundaries. The trial will be subjected to two interim analyses, which may result in early termination due to futility or early success. If the trial is not halted prematurely, it will proceed until it reaches a maximum of 312 patients. A total recruitment target of 348 (174 per group) should be planned to assess the primary 90-day endpoint assuming a 10% patient dropout rate.

Statistical analysis

The intention-to-treat analysis set will be used to examine the primary outcome. The primary analysis, known as the 'mRS shift' analysis, will employ an ordered logistic regression model. This model will treat the ordinal mRS Scale as the response variable and the treatment group as the explanatory variable, assuming proportional odds and a constant underlying treatment effect (OR) at all levels of the mRS Scale. Missing values will be imputed. Additionally, the primary analysis will be replicated in the per-protocol population. Secondary analyses include secondary and safety outcomes, along with subgroup analyses. While the study is not specifically designed or powered to test the hypotheses of these secondary analyses, two-sided p values will still be provided for comparison purposes between the treatment groups. This will help in facilitating the clinical interpretation of the results, even though the study's primary focus lies elsewhere. We will compare the rates of mRS 0–2 and 0–3 at 90 days, end procedure technical success, target vessel recanalisation at 18–36 hours, SICH and PH-2 within 18–36 hours, severe procedure-related complications, and new territory embolization within 18–36 hours using a generalised linear model. The relative risk (RR) and 95% CI will be presented. A general linear model will be used

to compare the differences in EQ-5D Score at 90 days, core infarct volume at 18–36 hours and NIHSS Score at 24 hours between treatment groups. The new ischaemic stroke in the downstream territory of the occluded vessel and mortality within 90 days will be compared between treatment groups using a Cox proportional hazard regression model, with HR and 95% CI. We will perform subgroup analyses on the influence on treatment effect by sex (male or female), age category (<65 or ≥65 years), occlusion site (anterior or posterior circulation), enrolment NIHSS (6–15 or ≥16 points), time to treatment (<6 or 6–24 hours), underlying ICAD (yes or no) and eTICI before randomisation (0–2a or 2b–3).

DISCUSSION

There is compelling evidence that establishes a connection between LVO recanalisation and increased odds of achieving a favourable clinical outcome. Successful MT in LVO cases has been shown to improve patient outcomes significantly. Conversely, when MT fails or LVO persists despite attempted treatment, the risk of mortality and long-term dependency is notably high. Even with new generation devices, that is, stent-retrievers and aspiration catheters, MT failed in about 12–41% of patients reported in previous RCTs. In the Chinese LVO population, we estimate that about 30% of MT procedures are unsuccessful, potentially attributable to a high rate of concurrent ICAD-related stenosis. In the absence of RCT data, experienced medical centres have explored the use of intracranial angioplasty as a potential rescue treatment.

The ANGEL-REOOT study is a phase III randomised, controlled trial that aims to evaluate the safety and efficacy of balloon dilation or permanent stenting in Chinese AIS–LVO patients with initially unsuccessful recanalisation (eTICI 0 to 2a) or severe residual stenosis (>70%) by MT. The primary outcome measure for this study is the functional status of the participants, which will be assessed at 90 days using the mRS.

The ANGEL-REOOT trial recruited its initial participant on 19 December 2021. As of 8 February 2023, a total of 306 subjects have been enrolled in the study. The study is projected to reach completion, including the collection of 90-day outcomes, by July 2023.

Summary and conclusions

ANGEL-REBOOT will provide new evidence regarding the necessity of angioplasty for failed MT. This will refine endovascular treatment in AIS–LVO patients from China as well as the global population.

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Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s)

Ethics approval This research will be carried out in accordance with the study protocol, the October 2013 Declaration of Helsinki, Chinese regulatory requirements/guidelines and other general regulatory requirements, for example, data protection laws and Good Clinical Practice guidelines. The study protocol and informed consent will be reviewed and approved by the relevant ethics committees (EC)/institutional review boards (IRB) and meet other country law requirements. The sponsor must provide written approval before any subject enrollment. The investigator will diligently submit reports to the EC/IRB for any modifications in the study protocol, as well as for any unanticipated problems that may pose risks to the human subjects or others involved in the research. Any changes to the research protocol will only be implemented after obtaining the necessary approvals from the EC/IRB, except in situations where immediate hazards to human subjects exist. This study involves human participants and was approved by IRB of Beijing Tiantan Hospital, Capital Medical University ID: KY2020-152-03 Participants gave informed consent to participate in the study before taking part.

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