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**Effect of Endovascular Treatment Alone Versus Intravenous Alteplase Plus
Endovascular Treatment on Functional Independence in Patients with
Acute Ischemic Stroke: The DEVT Randomized Clinical Trial**

Trial Protocol

This supplement contains the following items:

1. Original Trial Protocol (page 2 to 33)
2. Final Trial Protocol (page 34 to 65)
3. Summary of changes (page 66 to 68)

Note: personal identifying information has been redacted from the protocol documents to comply with international privacy legislation.

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33 **DEVT: A randomized, controlled, multicenter trial of direct endovascular treatment**
34 **versus standard bridging therapy for acute stroke patients with large vessel occlusion in**
35 **the anterior circulation**

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38 **Protocol Version: 1.0**

39 **Issue Date: 30th March 2018**

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List of Abbreviations

AE	Adverse Event
AIS	Acute Ischemia Stroke
ASITN/SIR	American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology
ASPECTS	Alberta Stroke Program Early Computed Tomography Score
BP	Blood Pressure
CEC	Clinical Events Committee
CRF	Case Report Form
CTA	Computed Tomographic Angiography
DEVT	Direct Endovascular Treatment Versus Standard Bridging Therapy in Large Artery Anterior Circulation Stroke
DSA	Digital Subtraction Angiography
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EQ-5D	European Quality Five Dimensions
EVT	Endovascular Treatment
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HCG	Human Chorionic Gonadotropin
HR	Heart Rate
ICA	Internal Carotid Artery
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-To-Treat
IVT	Intravenous Thrombolysis
LAR	Legally Authorized Representative
LVO	Large Vessel Occlusion
MCA	Middle Cerebral Artery
MR	Magnetic Resonance
MRA	Magnetic Resonance Angiography

mRS	Modified Rankin Scale
NCCT	Non-Contrast Computed Tomography
NIHSS	National Institutes of Health Stroke Scale
PP	Per-Protocol
QA	Quality Assurance
RCT	Randomized Controlled Trial
REB	Research Ethics Board
rt-PA	Recombinant Tissue-type Plasminogen Activator
SAE	Serious Adverse Event
SICH	Symptomatic Intracranial Hemorrhage
SOPs	Standard Operating Procedures
Temp	Temperature
TIA	Transient Ischemic Attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment

111 **Study Synopsis**

Trial Objectives	The objective is to determine whether endovascular treatment alone is non-inferior to intravenous thrombolysis bridging endovascular treatment in acute anterior circulation large vessel occlusive patients who are eligible for intravenous rt-PA.
Trial Design	This study is a randomized, controlled, multicenter trial with blinded outcome assessment. This trial uses a five-look group-sequential non-inferiority design. Up to 194 patients in each interim analysis will be consecutively randomized to endovascular treatment alone or rt-PA plus endovascular treatment group in 1:1 ratio over three years from about 35 hospitals in China.
Subjects	<p><u>Inclusion criteria</u></p> <ol style="list-style-type: none"> 1) Aged 18 years or older; 2) Presenting with acute ischemic stroke (AIS) symptom within 4.5 hours; 3) Eligible for IV rt-PA; 4) Occlusion of the intracranial internal carotid artery (ICA) or M1 segment of the middle cerebral artery (MCA) confirmed by CT or MR angiography (CTA or MRA); 5) Randomization no later than 4 hours 15 minutes after stroke symptom onset; 6) Informed consent obtained from patients or their legal representatives. <p><u>Exclusion criteria</u></p> <ol style="list-style-type: none"> 1) CT or MR evidence of hemorrhage (the presence of micro-bleeds is allowed); 2) Contraindications of IV rt-PA; 3) Pre-morbidity with a modified Rankin scale (mRS) score of ≥ 2; 4) Currently in pregnant or lactating or serum beta human chorionic gonadotrophin (HCG) test is positive on admission; 5) Contraindication to radiographic contrast agents, nickel, titanium metals or their alloys; 6) Arterial tortuosity and/or other arterial disease that would prevent the device from reaching the target vessel; 7) Patients with a preexisting neurological or psychiatric disease that would confound the neurological functional evaluations; 8) Subjects with occlusions in multiple vascular territories (e.g. bilateral anterior circulation, or anterior/posterior circulation); 9) CT or MRI evidence of mass effect or intracranial tumor (except small meningioma); 10) CT or MRI evidence of cerebral vasculitis; 11) CTA or MRA evidence of intracranial arteriovenous malformations or aneurysms; 12) Any terminal illness with life expectancy less than 6 months; 13) Unlikely to be available for 90-day follow-up; 14) Current participation in another clinical trial.
Treatments	Patients are assigned to receive either endovascular treatment (EVT) alone (primary-thrombectomy group) or rt-PA plus EVT (bridging-therapy group). In the bridging-therapy group, subjects will receive a single rt-PA dose of 0.9 mg/kg IV (maximum dose: 90 mg), with 10% given as a bolus, followed by continuous IV

		infusion of the rest dose within 1 hour. Simultaneously, EVT preparation should be initiated with or as soon as IV rt-PA administration. While in the primary-thrombectomy group, subjects will receive EVT directly without prior IV rt-PA. Subjects in both groups will undergo rapid EVT. EVT consisted of mechanical thrombectomy, thromboaspiration, balloon dilation, stenting, intra-arterial thrombolysis, or various combinations of these approaches.
Consent		Explicit written, signed informed consent from the subject or legally authorized representative will be obtained prior to any protocol specific procedures.
Randomization Method		Subjects will be randomly assigned in a 1:1 fashion to receive EVT alone or IV rt-PA plus EVT. Randomization occurs immediately after baseline (at the EVT institution) CT/MR brain imaging and CT/MR angiography via a real-time, internet-based randomization method. The randomization was stratified by participating centers.
Duration of Treatment		This study consists of one 90-day study period for each subject. Subjects will be hospitalized for care after their acute stroke according to the current standard of care. Subjects are required to return to clinic on Day 90 for end-of-study procedures.
Laboratory Tests		In order to support the assessment of patient safety baseline, chemistry laboratory tests will be completed. At baseline, blood work will be evaluated which includes: Blood cell counts, triglyceride, cholesterol, low density lipoprotein, high density lipoprotein, homocysteine, glucose, procalcitonin, HbA1C, prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, D-dimer, international normalized ratio. If the subject is female and is of childbearing potential, a pregnancy test (urine or serum point-of-care pregnancy test) must be completed and a negative test result obtained prior to inclusion in the trial. Electrocardiograms will also be collected and reviewed at baseline.
Assessment of Efficacy		The primary efficacy outcome is the overall proportion of subjects experiencing a functional independence 90 days post randomization, defined as a score of 0 to 2 on the mRS. The secondary efficacy outcomes include: 1) Proportion of mRS score 0 to 1 at 90 days; 2) Shift in the distribution of mRS scores at 90 days in EVT alone versus rt-PA plus EVT (ordinal shift analysis); 3) Successful recanalization proportion immediate after EVT. Successful recanalization is defined as a modified Treatment in Cerebral Infarction score of 2b (50 to 99% reperfusion) or 3 (complete reperfusion) in the post-procedure angiography; 4) Vessel recanalization rate evaluated by CTA or MRA within 48 hours; 5) The change of the National Institutes of Health Stroke Scale (NIHSS) score at 24 hours from baseline; 6) The change of the NIHSS score at 5-7 days or discharge if earlier from baseline;

	7) European Quality Five Dimensions (EQ-5D) scale score at 90 days.
Assessment of Safety	1) Symptomatic intracerebral hemorrhage (sICH) rate within 48 hours; 2) Mortality at 90 days; 3) Procedure-related complications such as arterial perforation, iatrogenic arterial dissection, arterial access site hematoma, and retroperitoneal hematoma; 4) Incidence of serious adverse events.

112

113

114 **Schedule of Assessments**

	Baseline	Day 1 (24 ± 12 h from randomization)	Day 2 (48 ± 8 h from randomization)	Day 5 or discharge (±1 d)	Day 90 (±14 d)
Informed consent	X				
History and examination	X				
Weight	X				
Vital Signs (BP, HR, Temp)	X	X	X	X	
Randomization	X				
NIHSS	X	X		X	
mRS	X*				X
ASPECTS	X				
EQ-5D					X
CBC, electrolytes, INR, aPTT, serum creatinine and serum glucose	X	X			
Pregnancy test‡	X				
NCCT/MR head	X		X**		
CTA/MRA	X		X		
ECG	X				
Endovascular Procedure	X				
sICH			X		
Mortality				X	X
AE assessment	Collected to Day 30 visit				
SAE assessment	Collected to Day 90 visit				
Prior medications	X				
Concomitant medications	Collected to Day 30 visit				

115 * Historical (pre-stroke) score.

116 ** MR head may be supplanted by an NCCT head if MR is unavailable.

117 ‡ If the subject is female and is of childbearing potential a pregnancy test (urine or serum point-of-care
 118 pregnancy test) must be completed and the result must be negative; this is the only mandatory laboratory test
 119 prior to randomization

120

121 **1. BACKGROUND INFORMATION**

122 Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) within 4.5 hours of symptom
123 onset is the first-line treatment for acute ischemic stroke(AIS)^{1,2}. Several randomized controlled trials have
124 consistently demonstrated that intravenous thrombolysis bridging with endovascular treatment (namely bridging
125 therapy) is superior to intravenous thrombolysis alone for acute anterior large vessel occlusion(LVO)³⁻⁹.
126 Intravenous thrombolysis prior to endovascular treatment can be initiated earlier, help eliminate thrombi in distal
127 or small arteries which are inaccessible for revascularization devices, facilitate mechanical thrombectomy, and
128 thereby increasing the rate of reperfusion^{10,11}. However, intravenous thrombolysis also has some drawbacks. For
129 instance, it may increase the risk of intracranial or systemic hemorrhage¹², especially when anti-thrombotic
130 therapy is administrated after angioplasty and/or stenting. It may also postpone endovascular treatment and
131 increase medical expenditures¹³. The therapeutic time window of intravenous thrombolysis is very narrow, which
132 has largely limited its application.

133 It remains uncertain whether pretreated with intravenous rt-PA provides any additional benefits to the acute
134 anterior large vessel occlusive patients experiencing endovascular treatment. A meta-analysis revealed that
135 patients treated with bridging therapy have higher recanalization rates, fewer device passes, equal probabilities
136 of symptomatic intracerebral hemorrhage, better clinical neurological outcomes, and lower mortality rates
137 compared with patients treated with direct endovascular treatment¹⁴. Whereas, a propensity score matching
138 analysis based on the Chinese population suggested that direct endovascular treatment can achieve similar
139 efficacy to that of bridging therapy, and a lower proportion of asymptomatic intracranial hemorrhage¹². However,
140 the baseline characteristics for the direct endovascular treatment group and bridging-therapy group of these
141 studies are lack of equipoise, which may have significant influence on the results. Prospective data on direct
142 endovascular treatment for acute anterior large vessel occlusion remains scarce. Thus, we propose the hypothesis
143 that EVT alone initiated within 4.5 h of stroke onset is not inferior to rt-PA plus EVT in acute stroke patients
144 with a proximal LVO in the anterior circulation.

145

146 **2. TRIAL OBJECTIVES**

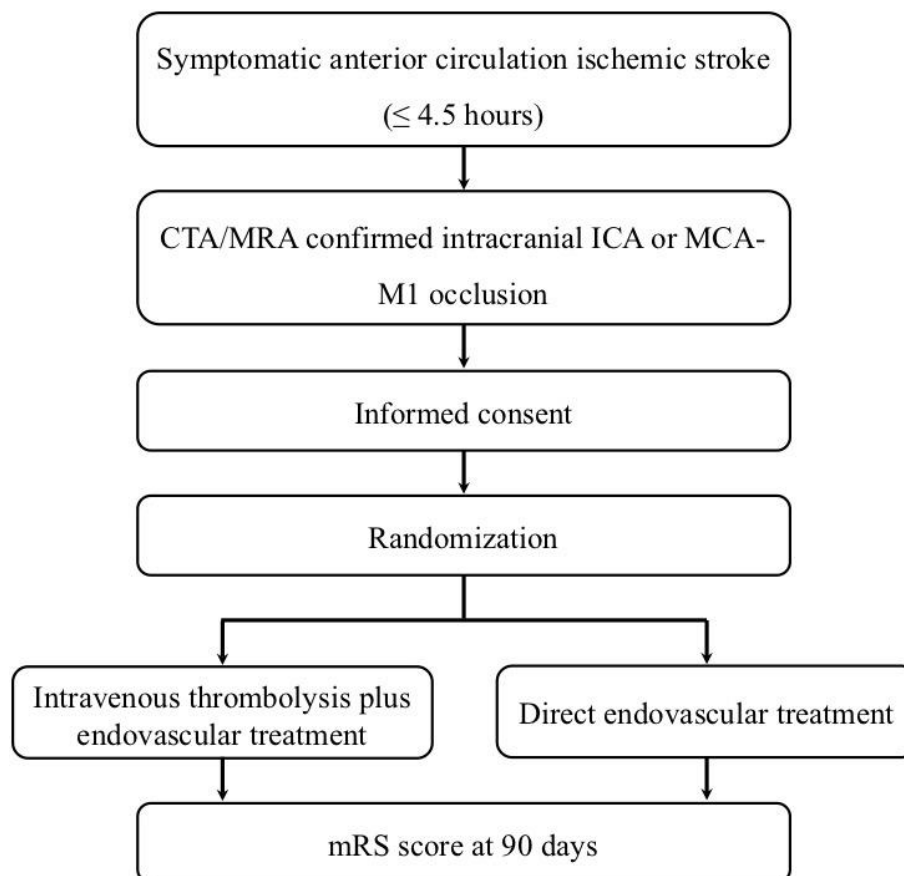
147 Direct Endovascular Treatment Versus Standard Bridging Therapy in Large Artery Anterior Circulation Stroke
148 (DEVT) Trial aims to investigate whether EVT alone is non-inferior to rt-PA plus EVT in acute anterior
149 circulation large vessel occlusive patients who are eligible for intravenous rt-PA.

150

151 **3. TRIAL DESIGN**

152 DEVT trial is a multicenter, prospective, randomized, open-label controlled clinical trial with blinded endpoint
153 evaluation. It is an academic trial designed by the principal investigators and a steering committee consisting of
154 experts in cerebrovascular diseases and interventional neuroradiology. The study patient flow outline was shown
155 in Figure 1.

156 Figure 1 Study flowchart of DEVT trial.



157

158 4. PATIENT POPULATION

159 4.1. Inclusion criteria

- 160 (1) Aged 18 years or older;
- 161 (2) Presenting with AIS symptom within 4.5 hours;
- 162 (3) Eligible for IV rt-PA;
- 163 (4) Occlusion of the intracranial internal carotid artery (ICA) or M1 segment of the middle cerebral artery
- 164 (MCA) confirmed by CT or MR angiography (CTA or MRA);
- 165 (5) Randomization no later than 4 hours 15 minutes after stroke symptom onset;
- 166 (6) Informed consent obtained from patients or their legal representatives.

167 4.2. Exclusion criteria

- 168 (1) CT or MR evidence of hemorrhage (the presence of micro-bleeds is allowed);
- 169 (2) Contraindications of IV rt-PA;
- 170 (3) Pre-morbidity with a modified Rankin scale (mRS) score of ≥ 2 ;
- 171 (4) Currently in pregnant or lactating or serum beta HCG test is positive on admission;
- 172 (5) Contraindication to radiographic contrast agents, nickel, titanium metals or their alloys;
- 173 (6) Arterial tortuosity and/or other arterial disease that would prevent the device from reaching the target
- 174 vessel;
- 175 (7) Patients with a preexisting neurological or psychiatric disease that would confound the neurological
- 176 functional evaluations;
- 177 (8) Subjects with occlusions in multiple vascular territories (e.g. bilateral anterior circulation, or
- 178 anterior/posterior circulation);
- 179 (9) CT or MRI evidence of mass effect or intracranial tumor (except small meningioma);
- 180 (10) CT or MRI evidence of cerebral vasculitis;

- 181 (11) CTA or MRA evidence of intracranial arteriovenous malformations or aneurysms;
182 (12) Any terminal illness with life expectancy less than 6 months;
183 (13) Unlikely to be available for 90-day follow-up;
184 (14) Current participation in another clinical trial.

185

186 **5. PARTICIPATING CENTER ELIGIBILITY**

187 To be fully eligible for participation in this trial, study centers were required have performed at least 80
188 endovascular procedures annually, including at least 50 thrombectomy procedures with the stent-retriever
189 devices. Moreover, all neurointerventionists with more than five years' experience in cerebrovascular
190 intervention and at least 10 cases of mechanical thrombectomy with stent retriever devices annually.

191

192 **6. RANDOMIZATION**

193 Subjects will be randomly assigned in a 1:1 fashion to receive EVT alone or IV rt-PA plus EVT. Randomization
194 occurs immediately after baseline (at the EVT institution) CT/MR brain imaging and CT/MR angiography via a
195 real-time, internet-based randomization method. The randomization was stratified by participating centers. The
196 time of randomization is defined as the time randomization occurred on the central server and this time is
197 considered time zero for the study. IV rt-PA will be infused immediately after randomization.

198 All subjects, investigators, their clinical staff, the clinical coordinating center, the data management group, and
199 the sponsor staff and delegates will be blinded to the randomization codes. The local laboratories will also be
200 blinded.

201

202 **7. TREATMENTS**

203 Patients are assigned to receive either EVT alone (primary-thrombectomy group) or rt-PA plus EVT
204 (bridging-therapy group). In the bridging-therapy group, subjects will receive a single rt-PA dose of 0.9 mg/kg
205 IV (maximum dose: 90 mg), with 10% given as a bolus, followed by continuous IV infusion of the rest dose
206 within 1 hour. Simultaneously, EVT preparation should be initiated with or as soon as IV rt-PA administration.
207 While in the primary-thrombectomy group, subjects will receive EVT alone without prior IV rt-PA. Subjects in
208 both groups will undergo rapid EVT. EVT consisted of mechanical thrombectomy, thromboaspiration, balloon
209 dilation, stenting, intra-arterial thrombolysis, or various combinations of these approaches. The choice of
210 technique is left to the discretion of the treating neurointerventionist. Additionally, stenting of the extracranial or
211 intracranial artery is permitted when absolutely necessary to obtain access to distal occlusion or to prevent acute
212 re-occlusion. This may require the use of thrombolytic agents to prevent acute stent thrombosis. After
213 recanalization of the target artery, all patients will get stroke unit care and postoperative management follows the
214 current American Heart Association/American Stroke Association guidelines¹⁵.

215 The use of conscious sedation or general anesthesia for the procedure to ensure the comfort and safety of patients
216 is at the discretion of the individual site neurointerventionalist. The steering committee will make
217 recommendations for dosages of thrombolytic agents, procedures, and for devices that will be considered in the
218 trial based on proposals by the executive committee or local investigators. The requirements for a device to be
219 considered in the trial should be approved by the China Food and Drug Administration or National Medical
220 Products Administration.

221

222 **8. OUTCOMES**

223 **8.1. Primary Efficacy Outcome**

224 The primary end-point is the overall proportion of subjects experiencing a functional independence 90 days post
225 randomization, defined as a score of 0 to 2 on the mRS. To ensure the reliability, evaluability, and traceability of

226 the mRS score, we keep patients' video or voice version of follow-up at 90 days except those who die or refuse
227 to take a video. The primary functional outcome is centrally assessed by two independent certified neurologists
228 in a blinded manner by the use of the video or voice recording. Disagreements are resolved by consensus.

229 **8.2. Secondary Efficacy Outcomes**

- 230 (1) Shift in the distribution of mRS scores at 90 days in EVT alone versus rt-PA plus EVT (ordinal shift
231 analysis);
- 232 (2) Proportion of mRS score 0 to 1 at 90 days;
- 233 (3) Successful recanalization proportion immediate after EVT. Successful recanalization is defined as a
234 modified Treatment in Cerebral Infarction score of 2b (50 to 99% reperfusion) or 3 (complete reperfusion)
235 in the post-procedure angiography¹⁶;
- 236 (4) Vessel recanalization rate evaluated by CTA or MRA within 48 hours;
- 237 (5) The change of the National Institutes of Health Stroke Scale (NIHSS) score at 24 hours from baseline¹⁷;
- 238 (6) The change of the NIHSS score at 5-7 days or discharge if earlier from baseline;
- 239 (7) European Quality Five Dimensions (EQ-5D) scale score at 90 days.

240 **8.3 Safety Outcomes**

- 241 (1) Symptomatic intracerebral hemorrhage (sICH) rate within 48 hours. ICH will be evaluated according to the
242 Heidelberg Bleeding Classification¹⁸. sICH was diagnosed if the new observed ICH was associated with
243 any of the following conditions: 1) NIHSS score increased more than 4 points than that immediately before
244 worsening; 2) NIHSS score increased more than 2 points in one category; 3) Deterioration led to intubation,
245 hemicraniectomy, external ventricular drain placement or any other major interventions. Additionally, the
246 symptom deteriorations could not be explained by causes other than the observed ICH. Hemicraniectomy
247 will be defined as that surgical procedure used to decompress the swollen hemisphere;
- 248 (2) Mortality at 90 days. Mortality rates are defined as the number of deaths observed divided by the number of
249 subject observed over the 90-day study period.
- 250 (3) Procedure-related complications such as arterial perforation, iatrogenic arterial dissection, embolization in
251 previously uninvolved vascular territory, arterial access site hematoma, and retroperitoneal hematoma.
252 Arterial perforation will be defined at angiography by the operator and associated with subarachnoid
253 hemorrhage. Iatrogenic arterial dissection will be defined at angiography by the operator. Arterial access
254 site hematoma will be assessed as a complication of arterial access puncture and defined by clinical
255 examination and anatomic imaging. Retroperitoneal hematoma will be assessed as a complication of groin
256 puncture and defined by imaging (ultrasound or CTA or MR). The definition of embolization in previously
257 uninvolved vascular territory is noted after recanalization of the primary occlusion site, any vessel
258 occlusions distal from the primary occlusion site were considered emboli due to periprocedural thrombus
259 fragmentation.
- 260 (4) Incidence of serious adverse events.

261

262 **9. BLINDING AND MASKING**

263 Each site will designate one or more physician(s) to perform the follow-up evaluation at 24 hours, 5-7 days or
264 discharge if earlier and at 90 days who cannot be involved in care of the subjects and must remain blinded to
265 treatment assignment of each subject.

266 Regarding the NIHSS examination at baseline, 24 hours, 5-7 days or discharge if earlier and the primary
267 end-point, first, a local independent neurologist, not involved in the trial patient management, will evaluate the
268 scores in a face to face clinical visit, recording the examination by video with the consent of patient or the legal
269 representative; and second, two experienced and certified physicians will centrally evaluate the score by using

270 the video recording. For cases with disagreement between the two assessors, decisions were made by the third
271 experienced neurologist.

272 All neuroimaging end-points including baseline Alberta Stroke Program Early Computed Tomography Score
273 (ASPECTS) score, recanalization within 48 hours, collateral circulation classification and hemorrhage will be
274 determined by the CT/MR core laboratory, which will be also blinded to treatment allocation. Another
275 independent angiographic core lab will review angiographic images from the procedure to determine clot
276 location and recanalization. Serious adverse events (SAEs) and procedure-related complications will be reviewed
277 and adjudicated by two individuals of the independent clinical events committee who will be blinded to
278 treatment allocation.

279

280 **10. ASSESSMENT OF EFFICACY**

281 **10.1. The Modified Rankin Scale**

282 The mRS is a valid and reliable clinician-reported measure of global disability that has been widely applied for
283 evaluating recovery from stroke. It is a scale used to measure functional recovery (the degree of disability or
284 dependence in daily activities) of people who have suffered a stroke^{19,20}. mRS scores range from 0 to 6, with 0
285 indicating no residual symptoms; 5 indicating bedbound, requiring constant care; and 6 indicating death. The
286 mRS will be obtained at Day 90. Premorbid mRS status will also be obtained retrospectively-at 24 Hours. The
287 mRS will only be scored by those trained and certified in the use of this scale.

288 **10.2. The National Institutes of Health Stroke Scale**

289 The NIHSS is a standardized neurological examination score that is a valid and reliable measure of disability and
290 recovery after acute stroke¹⁷. Scores range from 0 to 42, with higher scores indicating increasing severity. The
291 scale includes measures of level of consciousness, extra ocular movements, motor and sensory tests,
292 coordination, language and speech evaluations. The NIHSS will be administered at Baseline, at 24 hours from
293 baseline, Day 5-7or discharge. The NIHSS will only be scored by those trained and certified in the use of this
294 scale.

295 **10.3. EQ-5D**

296 The EQ-5D is a generic instrument for describing and valuing health. It is based on a descriptive system that
297 defines health in terms of five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and
298 Anxiety/Depression²¹. Each dimension has five response categories corresponding to: no problems, slight,
299 moderate, severe and extreme problems²². The instrument is designed for self-completion, and respondents also
300 rate their overall health on the day of the interview on a 0-100 hash-marked, vertical visual analogue scale. The
301 EQ- 5D will be administered on Day 90 by those trained in the use of this scale.

302

303 **11. ASSESSMENT OF SAFETY**

304 **11.1. Adverse Event Definitions**

305 **11.1.1. Adverse Event**

306 An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject
307 administered a pharmaceutical product and which does not necessarily have to have a causal relationship with
308 this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory
309 finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or
310 not considered related to the medicinal product.

311 Therefore, an AE may be: A new illness; The worsening of a concomitant illness; An effect of vaccination,
312 including the comparator; A combination of the above.

313 Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing condition worsens in
314 frequency or intensity, or if in the assessment of the treating physician there is a change in its clinical

315 significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes
316 of pre-existing conditions (e.g., asthma) if the frequency or intensity increases post-randomization.

317 11.1.2. Serious Adverse Event

318 A serious adverse event (SAE) is any untoward medical occurrence that at any dose: Result in death; Are
319 life-threatening; Require or prolong inpatient hospitalization; Result in persistent or significant
320 disability/incapacity, or; Are a congenital/birth defect.

321 A SAE can also be an important medical event that may not result in death, be life-threatening, or require
322 hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one
323 of the outcomes listed in this definition. For example, any new diagnosis of cancer (made after study enrollment)
324 is considered an important medical event. Because our primary safety outcomes for the trial are also SAEs by
325 definition, they will be reported dually as SAEs and as outcomes. SAEs should be managed according to the best
326 current standard of care.

327 All deaths occurring during the follow up to Day 90 will be reported as an SAE. When reporting a death, the
328 event or condition that caused or contributed to the fatal outcome should be reported as a single medical concept.
329 AE occurring within 30 days of randomization and all SAEs will be reported in the CRF. Severity and
330 relationship definitions are presented below.

331 11.2. Definitions of AE-Related Terms

AE Severity	
Mild	Awareness of sign or symptom but easily tolerated
Moderate	Discomfort sufficient to cause interference with normal activities.
Severe	Incapacitating, with inability to perform normal activities.
AE Relationship	
Related	A clinical event, including laboratory test abnormality, where there is a “reasonable possibility” that the SAE was caused by the study drug, meaning that there is evidence or arguments to suggest a causal relationship.
Probably	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.
Possibly	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unrelated	This category is applicable to AEs which are judged to be clearly and incontrovertibly due to extraneous causes (diseases, environment, etc.) and do not meet the criteria for drug relationship listed for the above-mentioned conditions.

332

333 12. CLINICAL MANAGEMENT OF ADVERSE EVENTS

334 12.1. Identification of Adverse Events by the Investigator

335 AE monitoring and reporting will be followed-up until Day 30. SAEs will be followed through the final study
336 exit visit (Day 90 Visit or death or end of study whichever is sooner) or until the subject is deemed “lost to
337 follow-up”.

338 AE identification while the subject is admitted to the acute stroke hospital will be collected via acute stroke
339 hospital patient records and verbal histories from the subject or legally authorized representative (LAR). For

340 follow up visits after discharge from the acute stroke hospital the subject (or LAR if the subject is not able to
341 respond to the questions) will be asked about the occurrence of AEs since the last contact, and if available, from
342 records at the acute stroke hospital. AEs that were ongoing at the last contact will be updated with a stop date or
343 confirmed as ongoing. AE collection will continue until Day 30, and SAE to Day 90 or the final contact.

344 A consistent methodology of eliciting AEs at all subject evaluation timepoints will be used. Non-directive
345 questions include: How have you felt since your last clinical visit/hospital discharge? Have you had any new or
346 changed health problems since you were last here? Have you had any unusual or unexpected worsening of your
347 underlying medical condition or overall health? Have there been any changes in the medicines you take since
348 your last clinical visit/hospital discharge?

349 Diagnosis versus signs and symptoms for the purpose of AE reporting: if known at the time of reporting, a
350 diagnosis should be reported rather than individual signs and symptoms. However, if a constellation of signs
351 and/or symptoms cannot be medically characterized as a single diagnosis it is acceptable to report the
352 information that is ultimately available.

353 **12.2. Reporting of Adverse Events**

354 AEs should be reported as they occur on the electronic Case Report Form (e-CRF). Documentation must be
355 supported by an entry in the subject's file. Each event should be described in detail along with start and stop
356 dates, severity, relationship to investigational product as judged by the investigator, action taken and outcome.

357 **12.3. Reporting of Serious Adverse Events**

358 In order to comply with current regulations on SAE reporting to health authorities, the investigator must
359 document all SAEs regardless of causal relationship and notify the Sponsor. The Investigator will give access
360 and provide the Sponsor with all necessary information to allow the Sponsor to conduct a detailed analysis of the
361 safety of the investigational product. It is the responsibility of the Investigator to request all necessary
362 documentation (e.g., medical records, discharge summary, autopsy) in order to provide comprehensive safety
363 information. All relevant information must then be transcribed into the e-SAE Form.

364 **12.4. Reporting by the Investigator**

365 All SAEs must be reported to the Sponsor within 24 hours of the local Investigator's first awareness of its
366 occurrence. SAEs will be reviewed by the trial medical monitor.

367 The investigator will report the SAEs using the e-SAE form in the e-CRF, which will send an immediate alert to
368 the Sponsor. If the e-CRF system is not available, a paper SAE form should be directed within 24 hours.

369 **12.5. Reporting SAEs to the Health Authorities and Ethics Committees**

370 The Sponsor will inform the relevant health authorities of any reportable SAEs according to the local regulatory
371 requirements. Reporting to the health authorities will be according to the Sponsor's standard operating
372 procedures.

373 SAEs that are assessed by the Sponsor to be unexpected and related to study drug (expedited reporting SAEs)
374 will be reported to the regulatory agencies as per country requirements. All other SAEs will be reported to
375 regulatory agencies based upon local reporting requirements.

376 The Sponsor's medical monitor or designee will notify the investigators in writing of the occurrence of any
377 reportable SAEs. The Sponsor or delegate will be responsible for reporting suspected unexpected serious adverse
378 reaction to any Central Ethics Committees in compliance with local current legislation. The investigators will be
379 responsible for informing their local ethics committees of any reportable SAEs as per their local requirements.

380

381 **13. DATA SAFETY MONITORING BOARD**

382 The independent Data safety monitoring board (DSMB) will be composed of an experienced neurologist, an
383 interventionalist, and a biostatistician, which are not involved in the trial. The DSMB will meet at least once a
384 year, and is provided with structured unmasked reports, prepared by the trial statistician, for their reference only.

385 DSMB is responsible for recommendations to the executive committee regarding stopping or extending the trial.
386 In addition, the DSMB will review the occurrence of SAEs and make recommendations to the executive
387 committee regarding safety of the trial.

388

389 **14. IMAGING CORE LABORATORY**

390 Centralized imaging core laboratories will be used in this trial to provide consistent assessment of all the images.
391 CT/MR and angiographic images will be independently reviewed by two independent central imaging core
392 laboratories respectively. CT/MR core laboratory will review CT/MR images obtained at baseline and within 24
393 hours for confirmation of inclusion criteria, ASPECTS score, collateral circulation classification, and
394 presence/absence of hemorrhage. Angiographic core laboratory will review angiographic images from the
395 procedure to determine clot location and recanalization. CT/MR core laboratory will be independent from the
396 angiographic core laboratory to ensure the CT/MR core laboratory is blinded to the treatment allocation.

397

398 **15. CLINICAL EVENTS COMMITTEE**

399 The Clinical events committee (CEC) will be comprised of three expert physicians independent of the
400 investigational sites. This committee will validate all the complications that occur over the course of the study
401 and categorized for severity and relatedness according to the definition in the Adverse Event section in the CEC
402 Manual of Operations. The CEC can request any additional source information and images supporting the
403 adverse events to assist with the adjudication.

404

405 **16. STATISTICS**

406 **16.1. Sample size estimates**

407 According to the previous study data^{12,23-25}, we hypothesis that the 90-day follow-up proportion of independent
408 functional outcome is 43% both in the primary-thrombectomy group and bridging-therapy group. The clinically
409 relevant non-inferiority margin Δ was -10.0%. To maintain the alpha, Pocock Analog Alpha Spending Function
410 is used. Sample size and power are computed incorporating a five-look group-sequential analysis plan with a
411 one-sided α at 0.025, 918 cases provide 80% power for testing the primary hypothesis of this trial; assuming the
412 attrition rate is 5% for the primary end-point, the total sample size is up to 970. The evaluable sample size is 194
413 at each interim analysis. Therefore, in each interim analysis, 97 cases should be enrolled in each treatment group.

414 **16.2. Analysis Populations**

415 **16.2.1. Intention-to-treat Population**

416 The primary efficacy analysis will be conducted in the intention-to-treat (ITT) population, defined as all subjects
417 randomized into the trial with grouping by randomized treatment, regardless of treatment actually received.
418 Deceased subject will be included in the ITT population with a mRS score of 6.

419 **16.2.2. Per Protocol Population**

420 The primary analysis will be repeated on the Per Protocol (PP) population, defined to be all subjects randomized
421 and treated, with no major protocol deviations. This population will be determined via blinded review of
422 protocol deviations at the end of the trial before database lock and unblinding. Prior to unblinding, the imaging
423 from each subject at the time of inclusion will be adjudicated to determine whether they have met the criteria for
424 endovascular intervention, and hence for the trial. This will include review of baseline NCCT and CTA. Subjects
425 who do not meet the imaging criteria outlined in the trial inclusion/exclusion criteria, will not be included in the
426 Per Protocol (PP) population.

427 Patients who withdraw informed consent immediately after randomization and are not to receive any treatment
428 should be excluded from all analysis populations.

429 **16.3. Analysis of Primary Efficacy Outcome**

430 Non-inferiority test will be used to test the primary hypothesis that the proportion of patients with independent
431 functional outcome will be non-inferior in the primary-thrombectomy group compared to the bridging-therapy
432 group. We desired a maximum of 5 looks when approximately 20, 40, 60, 80, and 100% of the total sample size
433 finish the follow-up, monitoring and data cleaning processes. A group-sequential test strategy was designed to
434 have reasonable chances of stopping as early as possible, either because of efficacy or safety reasons. The
435 independent DSMB may recommend stopping the trial either for effectiveness, or safety in case the stopping
436 boundaries are crossed at interim analysis. For shedding cases, follow-up will be performed until the end of the
437 study, and the results will be included in the final analysis. Statistical analysis will be performed on the SAS 9.3
438 system. Details of these are provided in the Statistical Analysis Plan.

439 **16.4. Analysis of secondary efficacy outcomes**

440 The key secondary outcomes will be tested in the following order:

- 441 1.The Proportion of mRS score 0 to 1 at 90 days;
- 442 2.Shift in the distribution of mRS scores at 90 days in EVT alone versus rt-PA plus EVT (ordinal shift analysis);
- 443 3.Successful recanalization proportion immediate after EVT.
- 444 4.Vessel recanalization rate evaluated by CTA or MRA within 48 hours;
- 445 5.The change of the National Institutes of Health Stroke Scale (NIHSS) score at 24 hours from baseline;
- 446 6.The change of the NIHSS score at 5-7 days or discharge if earlier from baseline;
- 447 7.European Quality Five Dimensions (EQ-5D) scale score at 90 days.

448 **16.5. Adjustment for covariates and subgroup analyses**

449 In addition to the primary and secondary analyses adjusting for age, sex, baseline NIHSS score, baseline
450 ASPECTS score, occlusion location, exploratory analyses will be conducted to determine the potential roles of
451 common baseline characteristics and assess potential heterogeneity of treatment effect across subgroups. Specific
452 subgroups of interest include the age ≥ 70 vs. < 70 years old, male vs. female, subject with different baseline
453 stroke severity (on NIHSS and measured radiologically on ASPECTS), baseline occlusion location (ICA
454 occlusion: no vs. yes), cause of stroke, onset to randomization time. Full details will be specified in detail in the
455 Statistical Analysis Plan.

456 **16.6. Handling of Missing Data**

457 Every effort will be made to keep missing data, particularly the Day 90 outcome assessments, to a minimum.
458 However, some missing data may be inevitable due to, for example, loss to follow-up. Deceased subject will
459 score 6 on the mRS and be counted as non-responders. For the primary analysis for regulatory submission, we
460 will assume that subject missing the primary endpoint data will be considered to be non-responders. Sensitivity
461 analyses using various imputation techniques will be specified prospectively in the Statistical Analysis Plan
462 before the database lock for the interim analysis if more than 5% of subject randomized are missing the primary
463 endpoint.

464 **16.7. Analyses of Safety**

465 The main analyses will be frequency of sICH and 90-day mortality. It is expected that the safety population and
466 the ITT population will be near-identical. Full details will be specified in detail in the Statistical Analysis Plan.

467

468 **17. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

469 The sponsor or delegate will be permitted to visit the study facilities at any reasonable time in order to maintain
470 current, detailed knowledge of the study through review of the records, source documents, observation, and
471 discussion of the conduct and progress of the study. In addition, the sponsor will maintain regular telephone and
472 written communication with all investigators through the coordinating center. The sponsor (or delegate) will be
473 given complete access to all components of the study facility that pertain to the conduct of this study, and may be
474 present to observe any aspect of the conduct of the study by medical and paramedical staff, including but not

475 limited to drug preparations, dosing, sample collections, and clinical observations. E-CRFs will be monitored
476 with sufficient frequency to assess the following: Subject randomization, compliance with protocol procedures,
477 the completeness and accuracy of data entered into the e-CRFs, verification of e-CRF data against original
478 source documents, and occurrence of AEs. Adequate time and all documents for these monitoring visits must be
479 made available by the investigators. The investigators will permit trial-related monitoring, audits, REB/IRB
480 review, and regulatory inspections, providing direct access to source data/documents.

481

482 **18. QUALITY CONTROL AND QUALITY ASSURANCE**

483 To ensure monitoring responsibilities are performed to the fullest extent possible, industry experienced study
484 monitors will perform on site data verification for the trial. All data monitored on site are verified for accuracy
485 and completeness using source documents for all subjects. In addition, 100% of subjects enrolled are monitored
486 for the presence of signed consent.

487 Monitoring of the investigational sites will be conducted by the sponsor or contracted to a qualified clinical
488 research organization. The sponsor will determine the extent, nature, and frequency of on-site visits that are
489 needed to ensure that the study is being conducted in accordance with the approved protocol (and any
490 amendments), Good Clinical Practice (GCP), and all applicable regulatory requirements. At site visits, the
491 monitor will, as required, assess the progress of the study; check that the study data chosen for verification are
492 authentic, accurate, and complete; verify that the safety and rights of patients are being protected; compare
493 original documents with data entered into the study database; and identify any issues and address their
494 resolution.

495 The investigator agrees to allow the monitor(s) direct access to all relevant documents, and to allocate his/her
496 time and the time of staff to discuss findings, corrective actions and any relevant issues. In addition to contacts
497 during the study, the monitor may also contact the site prior to the start of the study to discuss the protocol and
498 data collection procedures with site personnel.

499 Additional on-site monitoring verification includes: ongoing evaluation of the adequacy of site facilities and staff,
500 site recruitment, subject randomization, the presence of regulatory documents, and specific review of documents
501 and data. The initial performance-monitoring visit to a site takes place after the initial subject(s) are enrolled and
502 will continue according to enrolment for the duration of the trial.

503 During the monitoring visit, any omissions and corrections to data submitted to the database will be noted and
504 queries will be generated by the monitor and resolved by the site.

505 The close-out monitoring visit by the monitor will take place at the completion of subject enrollment and
506 protocol required follow-up visits at the performance site. At that visit, the monitor will again review the
507 presence of a regulatory file and verify documents for currency and completion as directed by the clinical
508 research unit. Sites will be instructed in the record retention of all trial documents. Principal Investigators are
509 directed to close the trial and issue a final report to the institutional review board. Finally, any additional special
510 considerations for the auditing of any additional safety issues are made during this final monitoring visit.

511 Except for an emergency situation in which proper care for the protection, safety and well- being of the study
512 subjects requires medical treatment, the study will be conducted as described in the approved protocol,
513 International Conference on Harmonization-Good Clinical Practice (ICH-GCP), Standard Operating Procedures
514 (SOPs) and regulatory requirements. All medical treatments will be recorded. Any deviation(s) from the protocol
515 will be recorded and presented in the final clinical study report.

516 **18.1. Audits and Inspections**

517 In accordance with the principles of ICH-GCP, the study site may be inspected by regulatory authorities. Quality
518 Assurance (QA) or their designates. The investigator and relevant clinical support staff will be required to be

519 actively involved in audits and inspections, including staff interviews, and to make all necessary documentation
520 and data available upon request.

521 During the course of the study and/or after it has been completed, one or more investigator site audits may be
522 undertaken by auditors. The purpose of these audits is to determine whether or not the study is being/has been
523 conducted and monitored in compliance with recognized ICH-GCP, protocol and approved amendment
524 requirements, applicable local SOPs, and local laws and regulations. It is the responsibility of the investigator
525 and site staff to promptly address any deficiencies stemming out of regulatory inspections and delegate audits,
526 and to ensure that agreed-upon corrective and preventive actions are implemented as soon as possible. An
527 inspection by any regulatory authority may occur at any time during or after completion of the study.

528 **18.2. Protocol Amendments and Revisions**

529 Should amendments and/or revisions to the protocol be required, they will be originated and documented by the
530 sponsor. All amendments and/or revisions will be made in compliance with sponsor SOPs. All amendments will
531 be submitted to the research ethics board/Institutional Review Board (REB/IRB) for approval prior to
532 implementation. It is the sponsor's responsibility to submit all revisions and amendments to regulatory
533 authorities when necessary.

534

535 **19. ETHICAL CONSIDERATION**

536 This research followed the ethical principles of the Helsinki Declaration. This protocol and the consent forms
537 will be submitted to each hospital's REB/IRB. Before initiation of the study, a copy of the REB/IRBs' approval
538 letters will be provided to the sponsor and the membership list of the REB/IRB will be kept on file. To make
539 sure the subjects fully understand about this trial, the investigators must provide the patients or their legal
540 representatives with detailed information about the clinical trial, including the purpose of the trial, possible
541 benefits and risks, and the rights/obligations. Subjects have the right to withdraw from the study at any time if
542 they wish to do so. The privacy protection of subjects has to be ensured. The patients or their legal
543 representatives give their written informed consent prior to the study. Each patient must leave contact
544 information to the investigator of the participating center. At the same time, the investigator must leave his own
545 phone number to the patient so that the patient can find the investigator at any time. Ethical approval for the
546 study was obtained by the Ethics Committee of the participating centers. SAEs will be reported to the REB/IRB
547 according to their requirements.

548

549 **20. DATA HANDLING AND RECORD KEEPING**

550 **20.1. Data Handling**

551 During the trial, clinical data reported in the e-CRFs will be integrated into the clinical database under the
552 responsibility of the Sponsor or their qualified representative. Quality control in the form of computerized logic
553 and/or consistency checks will be systematically applied in order to detect errors or omissions. In addition, safety
554 reviews may be performed several times by the Sponsor's staff in the course of the trial. Any questions
555 pertaining to the reported clinical data will be submitted to the investigator for resolution. Each step of this
556 process will be monitored through the implementation of individual passwords to maintain appropriate database
557 access and to ensure database integrity.

558 After integration of all corrections in the complete set of data, the database will be released for statistical
559 analysis.

560 **20.2. Investigator Files/Retention of Documents**

561 The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully
562 documented and the study data to be subsequently verified. These documents should be classified into two
563 different separate categories: Investigator's Study File; and Subject Clinical Source Documents.

564 The Investigator's Study File will contain the Protocol/Amendments, CRFs, REB/IRB and governmental
565 approval with correspondence, all versions of ethics approved informed consent forms, staff curriculum vitae
566 and authorization forms and other appropriate documents/correspondence, etc.

567 Subject clinical source documents (usually defined by the project in advance to record efficacy/safety parameters
568 independent of the CRFs) would include subject hospital/clinic records, physician's and nurse's notes,
569 appointment book, original laboratory reports, ECG, image data, signed consent forms, consultant letters, and
570 source worksheets. The investigator must keep these two categories of documents on file according to local
571 clinical trial regulation.

572 The Investigator and the sponsor will maintain the records of disposition of the drug and the clinic records in
573 accordance with ICH-GCP and each applicable regulatory agency. Clinic records will be retained at the site until
574 informed by the sponsor to destroy the documents. If the clinical study must be terminated for any reason, the
575 investigator will return all study materials to the sponsor and provide a written statement as to why the
576 termination has taken place and notify the REB/IRB.

577 **20.3. Source Documents and Background Data**

578 Any investigators shall supply the sponsor, upon request, with any required background data from the study
579 documentation or clinic records. This is particularly important when e-CRFs are illegible or when errors in data
580 transcription are suspected. In case of special problems and/or governmental queries or requests for audit
581 inspections, it is also necessary to have access to the complete study records, provided that subject
582 confidentiality is protected.

583 **20.4. Case Report Forms**

584 For each subject randomized, an e-CRF must be completed and signed by the investigator. If a subject withdraws
585 from the study, the reason must be noted on the CRF. All forms should be completed within five business days
586 of subject visit. All corrections will be tracked in the e-CRF audit trail. The Investigator should ensure the
587 accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all
588 required reports.

589 **20.5. Confidentiality**

590 All imaging, evaluation forms, reports, and other records that leave the site are identified only by the site and
591 subject number to maintain subject confidentiality. All records are kept in a locked file cabinet. Clinical
592 information is not released without written permission of the subject, except as necessary for monitoring by
593 REB/IRB, health authorities, the sponsor, or the sponsor's designee.

594 All study investigators at the clinical sites must ensure that the confidentiality of personal identity and all
595 personal medical information of study subjects are maintained at all times. clinical sites must conform to local
596 privacy and confidentiality law and custom. On the CRFs and other study documents or image materials
597 submitted to the CRU, the subjects are identified only by study identification codes.

598 Personal medical information may be reviewed for the purpose of verifying data recorded in the CRF by the site
599 monitors. Other properly authorized persons, such as the regulatory authorities, may also have access to these
600 records. Personal medical information is always treated as confidential.

601

602 **21. PUBLICATION AND PRESENTATION POLICY**

603 A trial executive committee shall be formed, and include at least the trial principal investigator and co-principal
604 investigator, the statistical consultant, and representatives of the Sponsor. The trial executive committee will be
605 co-authors on all publications and presentations. The primary author list for the primary publication will consist
606 of the executive committee and the site principal/qualified investigator at each of the sites. A formal publication
607 policy will be presented and developed by the trial executive.

608

609 22. DATA-SHARING PLAN

610 The sponsor will permit any and all academic publications arising from the trial data provided that no publication
611 containing unblinded trial data precedes publication of the overall trial results in a peer-review journal, and are
612 (1) approved by the trial executive committee and (2) the publication authors notify the sponsor at least 30 days
613 prior to submittal for publication with a copy of such proposed publication for the sponsor's review and
614 comment. Employees or consultants of the sponsor will only be named as authors in any such publication if the
615 parties agree that it is appropriate under the usual conventions used by academic institutions for naming authors
616 in scientific publications. Upon request of the sponsor the publication or disclosure shall be delayed for up to 60
617 days in order to allow for the filing of a patent application. The Executive Committee will make the trial results
618 available as free-access using PubMed and on Chinese Clinical Trials Registry. (www.chictr.org.cn).

619

620 23. STUDY ORGANIZATION AND FUNDING

621 DEVT trial is an investigator-initiated study which is organized by the second affiliated hospital of the Third
622 Military Medical University and conducted in about 30 comprehensive stroke centers in China. The authors
623 disclosed receipt of the following financial support: (1) National Science Fund for Distinguished Young Scholars
624 (No. 81525008), and (2) Major clinical innovation technology project of the Second Affiliated Hospital of the
625 Army Military Medical University (No. 2018JSLC0017). The funders had no involvement in the study design,
626 data collection, analysis and interpretation, writing or decision to submit the paper.

627

628 Appendix 1 – Classification of Subtype of Acute Ischemic Stroke

629 The TOAST classification system includes five categories: 1) large-artery atherosclerosis, 2) cardioembolism, 3)
630 small-artery occlusion (lacunae), 4) stroke of other determined etiology, and 5) stroke of undetermined etiology
631 (Table 1)²⁶. Diagnoses are based on clinical features and on data collected by tests such as brain imaging
632 (CT/MRI), cardiac imaging (echocardiography, etc.), duplex imaging of extracranial arteries, arteriography, and
633 laboratory assessments for a pro-thrombotic state.

634 The physician can apply the clinical and imaging findings when first assessing the patient and then consider the
635 results of other diagnostic tests later. An important part of the classification is the ability of the physician to
636 categorize a specific subtype diagnosis as probable or possible based on the degree of certainty. A "probable"
637 diagnosis is made if the clinical findings, neuroimaging data, and results of diagnostic studies are consistent with
638 one subtype and other etiologies have been excluded. A "possible" diagnosis is made when the clinical findings
639 and neuroimaging data suggest a specific subtype but other studies are not done. Because many patients will
640 have a limited number of diagnostic tests, the probable and possible subcategorizations allow the physician to
641 make as precise a subgroup diagnosis as can be achieved.

642 Large artery atherosclerosis

643 These patients will have clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of
644 a major brain artery or branch cortical artery, presumably due to atherosclerosis (Table 2). Clinical findings
645 include those of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem
646 or cerebellar dysfunction. A history of intermittent claudication, transient ischemic attacks (TIAs) in the same
647 vascular territory, a carotid bruit, or diminished pulses helps support the clinical diagnosis. Cortical or cerebellar
648 lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter on CT or MRI are
649 considered to be of potential large-artery atherosclerotic origin. Supportive evidence by duplex imaging or
650 arteriography of a stenosis of greater than 50% of an appropriate intracranial or extracranial artery is needed.
651 Diagnostic studies should exclude potential sources of cardiogenic embolism. The diagnosis of stroke secondary
652 to large artery atherosclerosis cannot be made if duplex or arteriographic studies are normal or show only
653 minimal changes.

654 Cardioembolism

655 This category includes patients with arterial occlusions presumably due to an embolus arising in the heart (Table
656 2). Cardiac sources are divided into high-risk and medium-risk groups based on the evidence of their relative
657 propensities for embolism (Table 3). At least one cardiac source for an embolus must be identified for a possible
658 or probable diagnosis of cardioembolic stroke. Clinical and brain imaging findings are similar to those described
659 for large-artery atherosclerosis. Evidence of a previous TIA or stroke in more than one vascular territory or
660 systemic embolism supports a clinical diagnosis of cardiogenic stroke. Potential large-artery atherosclerotic
661 sources of thrombosis or embolism should be eliminated. A stroke in a patient with a medium-risk cardiac source
662 of embolism and no other cause of stroke is classified as a possible cardioembolic stroke.

663 Small artery occlusion (lacunae)

664 This category includes patients whose strokes are often labeled as lacunar infarcts in other classifications (Table
665 2). The patient should have one of the traditional clinical lacunar syndromes and should not have evidence of
666 cerebral cortical dysfunction. A history of diabetes mellitus or hypertension supports the clinical diagnosis. The
667 patient should also have a normal CT/MRI examination or a relevant brain stem or subcortical hemispheric
668 lesion with a diameter of less than 1.5cm demonstrated. Potential cardiac sources for embolism should be absent,
669 and evaluation of the large extracranial arteries should not demonstrate a stenosis of greater than 50% in an
670 ipsilateral artery.

671 Acute stroke of other determined etiology

672 This category includes patients with rare causes of stroke, such as nonatherosclerotic vasculopathies,
 673 hypercoagulable states, or hematologic disorders. Patients in this group should have clinical and CT or MRI
 674 findings of an acute ischemic stroke, regardless of the size or location. Diagnostic studies such as blood tests or
 675 arteriography should reveal one of these unusual causes of stroke. Cardiac sources of embolism and large-artery
 676 atherosclerosis should be excluded by other studies.

677 **Stroke of undetermined etiology**

678 In several instances, the cause of a stroke cannot be determined with any degree of confidence. Some patients
 679 will have no likely etiology determined despite an extensive evaluation. In others, no cause is found but the
 680 evaluation was cursory. This category also includes patients with two or more potential causes of stroke so that
 681 the physician is unable to make a final diagnosis. For example, a patient with a medium-risk cardiac source of
 682 embolism who also has another possible cause of stroke identified would be classified as having a stroke of
 683 undetermined etiology. Other examples would be a patient who has atrial fibrillation and an ipsilateral stenosis
 684 of 50%, or the patient with a traditional lacunar syndrome and an ipsilateral carotid stenosis of 50%.

685

686 **TABLE 1. TOAST Classification of Subtypes of Acute Ischemic Stroke**

Large artery atherosclerosis (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacunae)*
Stroke of other determined etiology*
Stroke of undetermined etiology
a. Two or more causes identified
b. Negative evaluation
c. Incomplete evaluation

687 TOAST denotes Trial of Org 10172 in Acute Stroke Treatment.

688 *Possible or probable depending on results of ancillary studies.

689

690 **Table 2. Features of TOAST Classification of Subtypes of Ischemic Stroke**

Features	Subtype			
	Large artery atherosclerosis	Cardioembolism	Small artery occlusion (lacunae)	Other cause
Clinical				
Cortical or cerebellar dysfunction	+	+	-	+/-
Lacunar syndrome	-	-	+	+/-
Imaging				
Cortical, cerebellar, brain stem, or subcortical infarct > 1.5 cm	+	+	-	+/-

Subcortical or brain stem infarct < 1.5 cm	-	-	+/-	+/-
Tests				
Stenosis of extracranial internal carotid artery	+	-	-	-
Cardiac source of emboli	-	+	-	-
Other abnormality on tests	-	-	-	+

691

692 **TABLE 3. TOAST Classification of High- and Medium-Risk Sources of Cardioembolism****High-risk sources**

Mechanical prosthetic valve
 Mitral stenosis with atrial fibrillation
 Atrial fibrillation (other than lone atrial fibrillation)
 Left atrial/atrial appendage thrombus
 Sick sinus syndrome
 Recent myocardial infarction (<4 weeks)
 Left ventricular thrombus
 Dilated cardiomyopathy
 Akinetic left ventricular segment
 Atrial myxoma
 Infective endocarditis

Medium-risk sources

Mitral valve prolapse
 Mitral annulus calcification
 Mitral stenosis without atrial fibrillation
 Left atrial turbulence (smoke)
 Atrial septal aneurysm
 Patent foramen ovale
 Atrial flutter
 Lone atrial fibrillation
 Bioprosthetic cardiac valve
 Nonbacterial thrombotic endocarditis
 Congestive heart failure
 Hypokinetic left ventricular segment
 Myocardial infarction (> 4 weeks, < 6 months)

693

694 Appendix 2 - ASITN/SIR Collateral Vessel Grading System

695 Collateral vessel status was evaluated by using the American Society of Interventional and Therapeutic
696 Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral vessel grading system²⁷. Collateral
697 vessel scores were categorized into ASITN/SIR grades 0 or 1, 2, and 3 or 4. The following scoring system
698 provides a guide.

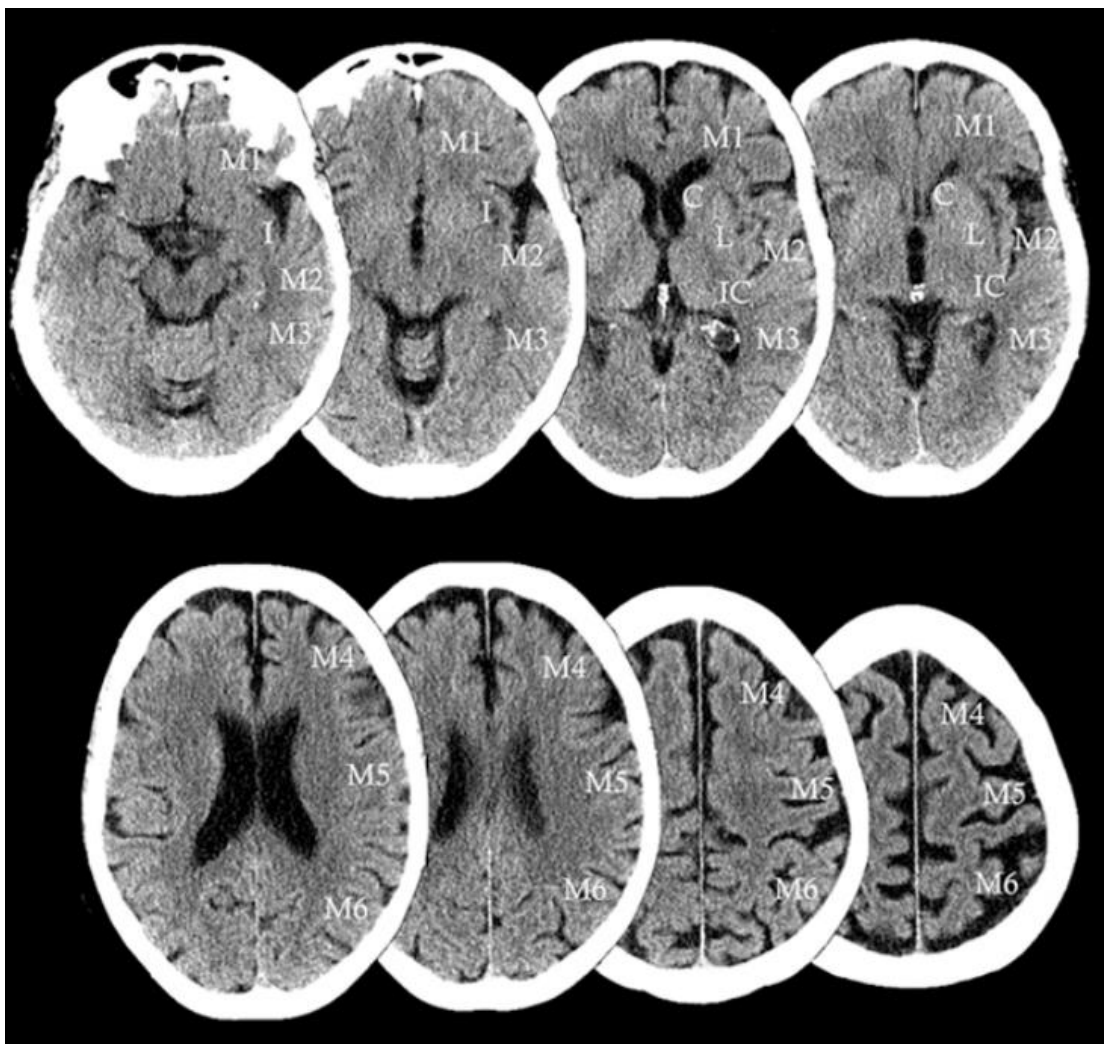
Grade	Description
0	No collateral vessels visible to the ischemic site
1	Slow collateral vessels to the periphery of the ischemic site with persistence of some of the defect
2	Rapid collateral vessels to periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory
3	Collateral vessels with slow but complete angiographic blood flow of the ischemic bed by the late venous phase
4	Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion

699

700

701 **Appendix 3 - The Alberta Stroke Program Early Computed Tomography Score (ASPECTS)**

702 NCCT shall be scored using ASPECTS, a 10-point score derived by examining each of 10 regions on the middle
703 cerebral artery territory²⁸. Ischemic change present is scored as 0; ischemic change absent is score as 1. Adding
704 up the score gives a maximum of 10 (favorable scan) and minimum of 0 (unfavorable scan). The score is highly
705 reliable when trichotomized into 0-4 (severe ischemic change, large core), 5-7 (moderate ischemic change) and
706 8-10 (minimal ischemic change, small core). ASPECTS may be less reliable early in stroke (i.e. within 90
707 minutes of onset); however, at later time windows it should be easy to recognize large areas of irreversible
708 damage. Having a good quality scan and optimization of scanner is key to successful interpretation. Further
709 information is available at: ww.aspectsinstroke.com.



710

711

712 **Appendix 4 - Modified Rankin Scale (MRS)**

Grade	Description ²⁹
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Death

713

714

715 **Appendix 5 - Modified Treatment In Cerebral Infarction (mTICI) Score**

Grade	Description ¹⁶
0	No perfusion
1	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
2a	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (e.g. in one major division of the middle cerebral artery (MCA) and its territory)
2b	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (e.g. in two major divisions of the MCA and their territories)
3	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

716

717

718 **Investigator’s Agreement**

719 I have read the attached protocol: a randomized, controlled, multicenter trial of Direct Endovascular treatment
720 Versus standard bridging Therapy for acute stroke patients with large vessel occlusion in the anterior circulation
721 (DEVT Trial), Version 1.0 dated 30th March 2018 and agree to abide by all provisions set forth therein. I agree
722 to comply with the current International Conference on Harmonization Guidelines for Good Clinical Practice
723 and the laws, rules, regulations and guidelines of the community, country, state or locality relating to the conduct
724 of the clinical study. I also agree that persons debarred from conducting or working on clinical studies by any
725 court or regulatory agency will not be allowed to conduct or work on studies for the sponsor.

726

727

728

729

730

731 Name Site Principal Investigator

Signature

732

733

734 Name of Clinical Site

Date

735

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818 **DEVT: A randomized, controlled, multicenter trial of direct endovascular treatment**
819 **versus standard bridging therapy for acute stroke patients with large vessel occlusion in**
820 **the anterior circulation**

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823 **Protocol Version: 2.0**

824 **Issue Date: 1st August 2019**

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895		

896 **List of Abbreviations**

AE	Adverse Event
AIS	Acute Ischemia Stroke
ASITN/SIR	American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology
ASPECTS	Alberta Stroke Program Early Computed Tomography Score
BP	Blood Pressure
CEC	Clinical Events Committee
CRF	Case Report Form
CTA	Computed Tomographic Angiography
DEVT	Direct Endovascular Treatment Versus Standard Bridging Therapy in Large Artery Anterior Circulation Stroke
DSA	Digital Subtraction Angiography
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EQ-5D-5L	European Quality Five-Dimension Five-Level
EVT	Endovascular Treatment
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HCG	Human Chorionic Gonadotropin
HR	Heart Rate
ICA	Internal Carotid Artery
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-To-Treat
IVT	Intravenous Thrombolysis
LAR	Legally Authorized Representative
LVO	Large Vessel Occlusion
MCA	Middle Cerebral Artery
MedDRA	Medical Dictionary for Regulatory Activities
MR	Magnetic Resonance

MRA	Magnetic Resonance Angiography
mRS	Modified Rankin Scale
NCCT	Non-Contrast Computed Tomography
NIHSS	National Institutes of Health Stroke Scale
PP	Per-Protocol
QA	Quality Assurance
RCT	Randomized Controlled Trial
REB	Research Ethics Board
rt-PA	Recombinant Tissue-type Plasminogen Activator
SAE	Serious Adverse Event
SICH	Symptomatic Intracranial Hemorrhage
SOC	System Organ Class
SOPs	Standard Operating Procedures
Temp	Temperature
TIA	Transient Ischemic Attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment

898 **Study Synopsis**

Trial Objectives	The objective is to determine whether endovascular treatment alone is non-inferior to intravenous thrombolysis bridging endovascular treatment in acute anterior circulation large vessel occlusive patients who are eligible for intravenous rt-PA.
Trial Design	This study is a randomized, controlled, multicenter trial with blinded outcome assessment. This trial uses a five-look group-sequential non-inferiority design. Up to 194 patients in each interim analysis will be consecutively randomized to endovascular treatment alone or rt-PA plus endovascular treatment group in 1:1 ratio over three years from about 35 hospitals in China.
Subjects	<p><u>Inclusion criteria</u></p> <ol style="list-style-type: none"> 1) Aged 18 years or older; 2) Presenting with acute ischemic stroke (AIS) symptom within 4.5 hours; 3) Eligible for IV rt-PA; 4) Occlusion of the intracranial internal carotid artery (ICA) or M1 segment of the middle cerebral artery (MCA) confirmed by CT or MR angiography (CTA or MRA); 5) Randomization no later than 4 hours 15 minutes after stroke symptom onset; 6) Informed consent obtained from patients or their legal representatives. <p><u>Exclusion criteria</u></p> <ol style="list-style-type: none"> 1) CT or MR evidence of hemorrhage (the presence of micro-bleeds is allowed); 2) Contraindications of IV rt-PA; 3) Pre-morbidity with a modified Rankin scale (mRS) score of ≥ 2; 4) Currently in pregnant or lactating or serum beta human chorionic gonadotrophin (HCG) test is positive on admission; 5) Contraindication to radiographic contrast agents, nickel, titanium metals or their alloys; 6) Arterial tortuosity and/or other arterial disease that would prevent the device from reaching the target vessel; 7) Patients with a preexisting neurological or psychiatric disease that would confound the neurological functional evaluations; 8) Subjects with occlusions in multiple vascular territories (e.g. bilateral anterior circulation, or anterior/posterior circulation); 9) CT or MRI evidence of mass effect or intracranial tumor (except small meningioma); 10) CT or MRI evidence of cerebral vasculitis; 11) CTA or MRA evidence of intracranial arteriovenous malformations or aneurysms; 12) Any terminal illness with life expectancy less than 6 months; 13) Unlikely to be available for 90-day follow-up; 14) Current participation in another clinical trial.
Treatments	Patients are assigned to receive either endovascular treatment (EVT) alone (primary-thrombectomy group) or rt-PA plus EVT (bridging-therapy group). In the bridging-therapy group, subjects will receive a single rt-PA dose of 0.9 mg/kg IV (maximum dose: 90 mg), with 10% given as a bolus, followed by continuous IV

	infusion of the rest dose within 1 hour. Simultaneously, EVT preparation should be initiated with or as soon as IV rt-PA administration. While in the primary-thrombectomy group, subjects will receive EVT directly without prior IV rt-PA. Subjects in both groups will undergo rapid EVT. EVT consisted of mechanical thrombectomy, thromboaspiration, balloon dilation, stenting, intra-arterial thrombolysis, or various combinations of these approaches.
Consent	Explicit written, signed informed consent from the subject or legally authorized representative will be obtained prior to any protocol specific procedures.
Randomization Method	Subjects will be randomly assigned in a 1:1 fashion to receive EVT alone or rt-PA plus EVT. Randomization occurs immediately after baseline (at the EVT institution) CT/MR brain imaging and CT/MR angiography via a real-time, internet-based randomization method. The randomization was stratified by participating centers.
Duration of Treatment	This study consists of one 90-day study period for each subject. Subjects will be hospitalized for care after their acute stroke according to the current standard of care. Subjects are required to return to clinic on Day 90 for end-of-study procedures.
Laboratory Tests	In order to support the assessment of patient safety baseline, chemistry laboratory tests will be completed. At baseline, blood work will be evaluated which includes: Blood cell counts, triglyceride, cholesterol, low density lipoprotein, high density lipoprotein, homocysteine, glucose, procalcitonin, HbA1C, prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, D-dimer, international normalized ratio. If the subject is female and is of childbearing potential, a pregnancy test (urine or serum point-of-care pregnancy test) must be completed and a negative test result obtained prior to inclusion in the trial. Electrocardiograms will also be collected and reviewed at baseline.
Assessment of Efficacy	The primary efficacy outcome is the overall proportion of subjects experiencing a functional independence 90 days post randomization, defined as a score of 0 to 2 on the mRS. The secondary efficacy outcomes include: <ol style="list-style-type: none"> 1) Proportion of mRS score 0 to 1 at 90 days; 2) Shift in the distribution of mRS scores at 90 days in EVT alone versus rt-PA plus EVT (ordinal shift analysis); 3) Successful recanalization proportion immediate after EVT. Successful recanalization is defined as a modified Treatment in Cerebral Infarction score of 2b (substantial perfusion), 2c (near-complete perfusion) or 3 (complete reperfusion) in the post-procedure angiography; 4) Vessel recanalization rate evaluated by CTA or MRA within 48 hours; 5) The change of the National Institutes of Health Stroke Scale (NIHSS) score at 24 hours from baseline; 6) The change of the NIHSS score at 5-7 days or discharge if earlier from baseline; 7) European Quality Five-Dimension Five-Level (EQ-5D-5L) scale score at 90

	days.
Assessment of Safety	1) Symptomatic intracerebral hemorrhage (sICH) rate within 48 hours; 2) Mortality at 90 days; 3) Procedure-related complications such as arterial perforation, iatrogenic arterial dissection, arterial access site hematoma, and retroperitoneal hematoma; 4) Incidence of serious adverse events.

899

900

901 **Schedule of Assessments**

	Baseline	Day 1 (24 ± 12 h from randomization)	Day 2 (48 ± 8 h from randomization)	Day 5 or discharge (±1 d)	Day 90 (±14 d)
Informed consent	X				
History and examination	X				
Weight*	X				
Vital Signs (BP, HR, Temp)	X	X	X	X	
Randomization	X				
NIHSS	X	X		X	
mRS	X*				X
ASPECTS	X				
EQ-5D-5L					X
CBC, electrolytes, INR, aPTT, serum creatinine and serum glucose	X	X			
Pregnancy test‡	X				
NCCT/MR head	X		X**		
CTA/MRA	X		X		
ECG	X				
Endovascular Procedure	X				
sICH			X		
Mortality				X	X
AE assessment	Collected to Day 30 visit				
SAE assessment	Collected to Day 90 visit				
Prior medications§	X				
Concomitant medications§	Collected to Day 30 visit				

902 * The subject's actual weight will be measured in hospital using standard hospital scales (i.e., stand up or in-bed
903 scales if the subject is not ambulatory). If actual weight cannot be measured for any reason (due to, for
904 example severe illness or unavailability of in-bed scales at the site), weight will be determined by first asking
905 the subject, second asking a family member or third by estimation.

906 * Historical (pre-stroke) score.

907 ** MR head may be supplanted by an NCCT head if MR is unavailable.

908 ‡ If the subject is female and is of childbearing potential a pregnancy test (urine or serum point-of-care
909 pregnancy test) must be completed and the result must be negative; this is the only mandatory laboratory test
910 prior to randomization

911 § Prior and concomitant medications will be listed per patient, with the listings separated within treatment group.

912

913 1. BACKGROUND INFORMATION

914 Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) within 4.5 hours of symptom
915 onset is the first-line treatment for acute ischemic stroke(AIS)^{1,2}. Several randomized controlled trials have
916 consistently demonstrated that intravenous thrombolysis bridging with endovascular treatment (namely bridging
917 therapy) is superior to intravenous thrombolysis alone for acute anterior large vessel occlusion(LVO)³⁻⁹.
918 Intravenous thrombolysis prior to endovascular treatment can be initiated earlier, help eliminate thrombi in distal
919 or small arteries which are inaccessible for revascularization devices, facilitate mechanical thrombectomy, and
920 thereby increasing the rate of reperfusion^{10,11}. However, intravenous thrombolysis also has some drawbacks. For
921 instance, it may increase the risk of intracranial or systemic hemorrhage¹², especially when anti-thrombotic
922 therapy is administrated after angioplasty and/or stenting. It may also postpone endovascular treatment and
923 increase medical expenditures¹³. The therapeutic time window of intravenous thrombolysis is very narrow, which
924 has largely limited its application. In addition, IVT before EVT is associated with an increased incidence of clot
925 migration, resulting in an increased rate of clots inaccessibility by mechanical thrombectomy¹⁴.

926 It remains uncertain whether pretreated with intravenous rt-PA provides any additional benefits to the acute
927 anterior large vessel occlusive patients experiencing endovascular treatment. A meta-analysis revealed that
928 patients treated with bridging therapy have higher recanalization rates, fewer device passes, equal probabilities
929 of symptomatic intracerebral hemorrhage, better clinical neurological outcomes, and lower mortality rates
930 compared with patients treated with direct endovascular treatment¹⁵. Whereas, a propensity score matching
931 analysis based on the Chinese population suggested that direct endovascular treatment can achieve similar
932 efficacy to that of bridging therapy, and a lower proportion of asymptomatic intracranial hemorrhage¹². Another
933 meta-analysis showed that direct endovascular treatment may carries comparable effectiveness and safety as
934 compared with bridging therapy by pooling studies with lower selection bias¹⁶. However, the baseline
935 characteristics for the direct endovascular treatment group and bridging-therapy group of these studies are lack
936 of equipoise, which may have significant influence on the results. Prospective data on direct endovascular
937 treatment for acute anterior large vessel occlusion remains scarce. Thus, we propose the hypothesis that EVT
938 alone initiated within 4.5 h of stroke onset is not inferior to rt-PA plus EVT in acute stroke patients with a
939 proximal LVO in the anterior circulation.

940

941 2. TRIAL OBJECTIVES

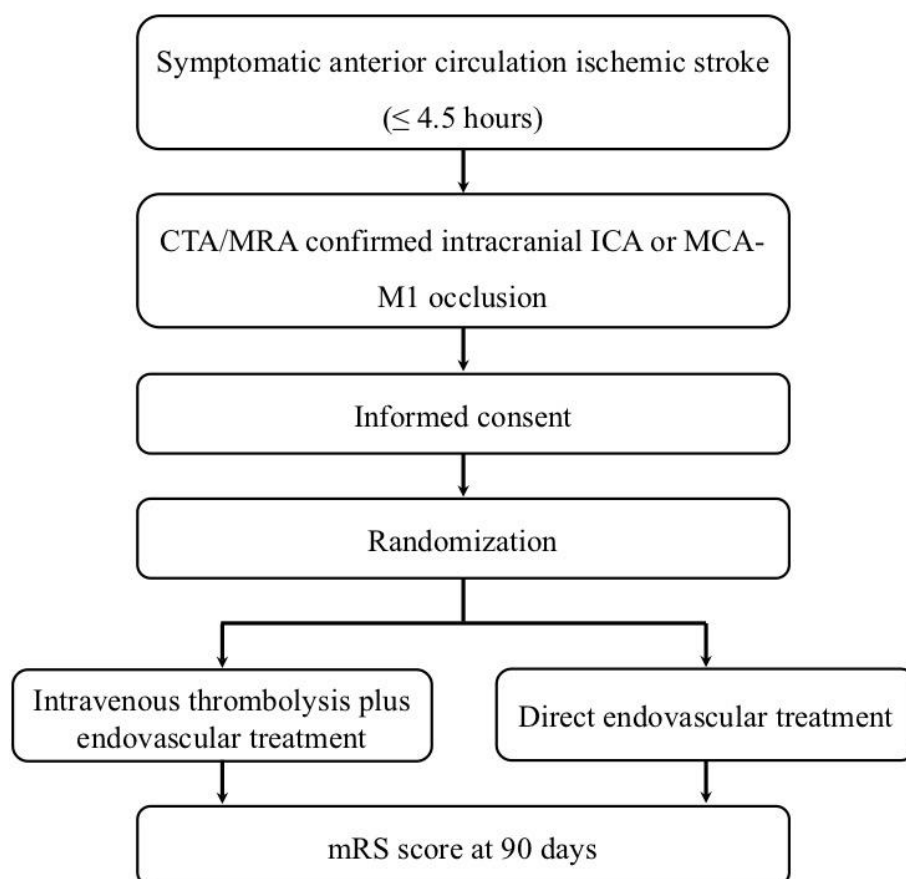
942 Direct Endovascular Treatment Versus Standard Bridging Therapy in Large Artery Anterior Circulation Stroke
943 (DEVT) Trial aims to investigate whether EVT alone is non-inferior to rt-PA plus EVT in acute anterior
944 circulation large vessel occlusive patients who are eligible for intravenous rt-PA.

945

946 3. TRIAL DESIGN

947 DEVT trial is a multicenter, prospective, randomized, open-label controlled clinical trial with blinded endpoint
948 evaluation. It is an academic trial designed by the principal investigators and a steering committee consisting of
949 experts in cerebrovascular diseases and interventional neuroradiology. The study patient flow outline was shown
950 in Figure 1.

951 Figure 1 Study flowchart of DEVT trial.



952

953 **4. PATIENT POPULATION**954 **4.1. Inclusion criteria**

- 955 (1) Aged 18 years or older;
- 956 (2) Presenting with AIS symptom within 4.5 hours;
- 957 (3) Eligible for IV rt-PA;
- 958 (4) Occlusion of the intracranial internal carotid artery (ICA) or M1 segment of the middle cerebral artery
- 959 (MCA) confirmed by CT or MR angiography (CTA or MRA);
- 960 (5) Randomization no later than 4 hours 15 minutes after stroke symptom onset;
- 961 (6) Informed consent obtained from patients or their legal representatives.

962 **4.2. Exclusion criteria**

- 963 (1) CT or MR evidence of hemorrhage (the presence of micro-bleeds is allowed);
- 964 (2) Contraindications of IV rt-PA;
- 965 (3) Pre-morbidity with a modified Rankin scale (mRS) score of ≥ 2 ;
- 966 (4) Currently in pregnant or lactating or serum beta HCG test is positive on admission;
- 967 (5) Contraindication to radiographic contrast agents, nickel, titanium metals or their alloys;
- 968 (6) Arterial tortuosity and/or other arterial disease that would prevent the device from reaching the target
- 969 vessel;
- 970 (7) Patients with a preexisting neurological or psychiatric disease that would confound the neurological
- 971 functional evaluations;
- 972 (8) Subjects with occlusions in multiple vascular territories (e.g. bilateral anterior circulation, or
- 973 anterior/posterior circulation);
- 974 (9) CT or MRI evidence of mass effect or intracranial tumor (except small meningioma);
- 975 (10) CT or MRI evidence of cerebral vasculitis;

- 976 (11) CTA or MRA evidence of intracranial arteriovenous malformations or aneurysms;
977 (12) Any terminal illness with life expectancy less than 6 months;
978 (13) Unlikely to be available for 90-day follow-up;
979 (14) Current participation in another clinical trial.

980

981 **5. PARTICIPATING CENTER ELIGIBILITY**

982 To be fully eligible for participation in this trial, study centers are required have performed at least 80
983 endovascular procedures annually, including at least 50 thrombectomy procedures with the stent-retriever
984 devices. Moreover, all neurointerventionists with more than five years' experience in cerebrovascular
985 intervention and at least 10 cases of mechanical thrombectomy with stent retriever devices annually.

986

987 **6. RANDOMIZATION**

988 Subjects will be randomly assigned in a 1:1 fashion to receive EVT alone or IV rt-PA plus EVT. Randomization
989 occurs immediately after baseline (at the EVT institution) CT/MR brain imaging and CT/MR angiography via a
990 real-time, internet-based randomization method. The randomization was stratified by participating centers. The
991 time of randomization is defined as the time randomization occurred on the central server and this time is
992 considered time zero for the study. IV rt-PA will be infused immediately after randomization.

993 All subjects, investigators, their clinical staff, the clinical coordinating center, the data management group, and
994 the sponsor staff and delegates will be blinded to the randomization codes. The local laboratories will also be
995 blinded.

996

997 **7. TREATMENTS**

998 Patients are assigned to receive either EVT alone (primary-thrombectomy group) or rt-PA plus EVT
999 (bridging-therapy group). In the bridging-therapy group, subjects will receive a single rt-PA dose of 0.9 mg/kg
1000 IV (maximum dose: 90 mg), with 10% given as a bolus, followed by continuous IV infusion of the rest dose
1001 within 1 hour. Simultaneously, EVT preparation should be initiated with or as soon as IV rt-PA administration.
1002 While in the primary-thrombectomy group, subjects will receive EVT alone without prior IV rt-PA. Subjects in
1003 both groups will undergo rapid EVT. EVT consisted of mechanical thrombectomy, thromboaspiration, balloon
1004 dilation, stenting, intra-arterial thrombolysis, or various combinations of these approaches. The choice of
1005 technique is left to the discretion of the treating neurointerventionist. Additionally, stenting of the extracranial or
1006 intracranial artery is permitted when absolutely necessary to obtain access to distal occlusion or to prevent acute
1007 re-occlusion. This may require the use of thrombolytic agents to prevent acute stent thrombosis. After
1008 recanalization of the target artery, all patients will get stroke unit care and postoperative management follows the
1009 current American Heart Association/American Stroke Association guidelines¹⁷.

1010 The use of conscious sedation or general anesthesia for the procedure to ensure the comfort and safety of patients
1011 is at the discretion of the individual site neurointerventionalist. The steering committee will make
1012 recommendations for dosages of thrombolytic agents, procedures, and for devices that will be considered in the
1013 trial based on proposals by the executive committee or local investigators. The requirements for a device to be
1014 considered in the trial should be approved by the China Food and Drug Administration or National Medical
1015 Products Administration.

1016

1017 **8. OUTCOMES**

1018 **8.1. Primary Efficacy Outcome**

1019 The primary end-point is the overall proportion of subjects experiencing a functional independence 90 days post
1020 randomization, defined as a score of 0 to 2 on the mRS. To ensure the reliability, evaluability, and traceability of

1021 the mRS score, we keep patients' video or voice version of follow-up at 90 days except those who die or refuse
1022 to take a video. The primary functional outcome is centrally assessed by two independent certified neurologists
1023 in a blinded manner by the use of the video or voice recording. Disagreements are resolved by consensus.

1024 **8.2. Secondary Efficacy Outcomes**

- 1025 (1) Shift in the distribution of mRS scores at 90 days in EVT alone versus rt-PA plus EVT (ordinal shift
1026 analysis);
- 1027 (2) Proportion of mRS score 0 to 1 at 90 days;
- 1028 (3) Successful recanalization proportion immediate after EVT. Successful recanalization is defined as an
1029 expanded Thrombolysis In Cerebral Infarction score of 2b (substantial perfusion), 2c (near-complete
1030 perfusion) or 3 (complete reperfusion) in the post-procedure angiography¹⁸;
- 1031 (4) Vessel recanalization rate evaluated by CTA or MRA within 48 hours;
- 1032 (5) The change of the National Institutes of Health Stroke Scale (NIHSS) score at 24 hours from baseline¹⁹;
- 1033 (6) The change of the NIHSS score at 5-7 days or discharge if earlier from baseline;
- 1034 (7) European Quality Five-Dimension Five-Level (EQ-5D-5L) scale score at 90 days.

1035 **8.3 Safety Outcomes**

- 1036 (1) Symptomatic intracerebral hemorrhage (sICH) rate within 48 hours. ICH will be evaluated according to the
1037 Heidelberg Bleeding Classification²⁰. sICH was diagnosed if the new observed ICH was associated with
1038 any of the following conditions: 1) NIHSS score increased more than 4 points than that immediately before
1039 worsening; 2) NIHSS score increased more than 2 points in one category; 3) Deterioration led to intubation,
1040 hemicraniectomy, external ventricular drain placement or any other major interventions. Additionally, the
1041 symptom deteriorations could not be explained by causes other than the observed ICH. Hemicraniectomy
1042 will be defined as that surgical procedure used to decompress the swollen hemisphere;
- 1043 (2) Mortality at 90 days. Mortality rates are defined as the number of deaths observed divided by the number of
1044 subject observed over the 90-day study period;
- 1045 (3) Procedure-related complications such as arterial perforation, iatrogenic arterial dissection, embolization in
1046 previously uninvolved vascular territory, arterial access site hematoma, and retroperitoneal hematoma.
1047 Arterial perforation will be defined at angiography by the operator and associated with subarachnoid
1048 hemorrhage. Iatrogenic arterial dissection will be defined at angiography by the operator. Arterial access
1049 site hematoma will be assessed as a complication of arterial access puncture and defined by clinical
1050 examination and anatomic imaging. Retroperitoneal hematoma will be assessed as a complication of groin
1051 puncture and defined by imaging (ultrasound or CTA or MR). The definition of embolization in previously
1052 uninvolved vascular territory is noted after recanalization of the primary occlusion site, any vessel
1053 occlusions distal from the primary occlusion site are considered emboli due to periprocedural thrombus
1054 fragmentation.
- 1055 (4) Incidence of serious adverse events.

1056

1057 **9. BLINDING AND MASKING**

1058 Each site will designate one or more physician(s) to perform the follow-up evaluation at 24 hours, 5-7 days or
1059 discharge if earlier and at 90 days who cannot be involved in care of the subjects and must remain blinded to
1060 treatment assignment of each subject.

1061 Regarding the NIHSS examination at baseline, 24 hours, 5-7 days or discharge if earlier and the primary
1062 end-point, first, a local independent neurologist, not involved in the trial patient management, will evaluate the
1063 scores in a face to face clinical visit, recording the examination by video with the consent of patient or the legal
1064 representative; and second, two experienced and certified physicians will centrally evaluate the score by using

1065 the video recording. For cases with disagreement between the two assessors, decisions are made by the third
1066 experienced neurologist.

1067 All neuroimaging end-points including baseline Alberta Stroke Program Early Computed Tomography Score
1068 (ASPECTS) score, recanalization within 48 hours, collateral circulation classification and hemorrhage will be
1069 determined by the CT/MR core laboratory, which will be also blinded to treatment allocation. Another
1070 independent angiographic core lab will review angiographic images from the procedure to determine clot
1071 location and recanalization. Serious adverse events (SAEs) and procedure-related complications will be reviewed
1072 and adjudicated by two individuals of the independent clinical events committee who will be blinded to
1073 treatment allocation.

1074

1075 **10. ASSESSMENT OF EFFICACY**

1076 **10.1. The Modified Rankin Scale**

1077 The mRS is a valid and reliable clinician-reported measure of global disability that has been widely applied for
1078 evaluating recovery from stroke. It is a scale used to measure functional recovery (the degree of disability or
1079 dependence in daily activities) of people who have suffered a stroke^{21,22}. mRS scores range from 0 to 6, with 0
1080 indicating no residual symptoms; 5 indicating bedbound, requiring constant care; and 6 indicating death. The
1081 mRS will be obtained at Day 90. Premorbid mRS status will also be obtained retrospectively and reported on the
1082 24h CRF page. The mRS will only be scored by those trained and certified in the use of this scale.

1083 **10.2. The National Institutes of Health Stroke Scale**

1084 The NIHSS is a standardized neurological examination score that is a valid and reliable measure of disability and
1085 recovery after acute stroke¹⁹. Scores range from 0 to 42, with higher scores indicating increasing severity. The
1086 scale includes measures of level of consciousness, extra ocular movements, motor and sensory tests,
1087 coordination, language and speech evaluations. The NIHSS will be administered at Baseline, at 24 hours from
1088 baseline, Day 5-7or discharge. The NIHSS will only be scored by those trained and certified in the use of this
1089 scale.

1090 **10.3. EQ-5D-5L**

1091 The EQ-5D-5L is a generic instrument for describing and valuing health. It is based on a descriptive system that
1092 defines health in terms of five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and
1093 Anxiety/Depression²³. Each dimension has five response categories corresponding to: no problems, slight,
1094 moderate, severe and extreme problems. The instrument is designed for self-completion, and respondents also
1095 rate their overall health on the day of the interview on a 0-100 hash-marked, vertical visual analogue scale. The
1096 EQ-5D-5L will be administered on Day 90 by those trained in the use of this scale.

1097

1098 **11. ASSESSMENT OF SAFETY**

1099 **11.1. Adverse Event Definitions**

1100 **11.1.1. Adverse Event**

1101 An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject
1102 administered a pharmaceutical product and which does not necessarily have to have a causal relationship with
1103 this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory
1104 finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or
1105 not considered related to the medicinal product.

1106 Therefore, an AE may be: A new illness; The worsening of a concomitant illness; An effect of vaccination,
1107 including the comparator; A combination of the above.

1108 Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing condition worsens in
1109 frequency or intensity, or if in the assessment of the treating physician there is a change in its clinical

1110 significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes
1111 of pre-existing conditions (e.g., asthma) if the frequency or intensity increases post-randomization.

1112 11.1.2. Serious Adverse Event

1113 A serious adverse event (SAE) is any untoward medical occurrence that at any dose: Result in death; Are
1114 life-threatening; Require or prolong inpatient hospitalization; Result in persistent or significant
1115 disability/incapacity, or; Are a congenital/birth defect.

1116 A SAE can also be an important medical event that may not result in death, be life-threatening, or require
1117 hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one
1118 of the outcomes listed in this definition. For example, any new diagnosis of cancer (made after study enrollment)
1119 is considered an important medical event. Because our primary safety outcomes for the trial are also SAEs by
1120 definition, they will be reported dually as SAEs and as outcomes. SAEs should be managed according to the best
1121 current standard of care.

1122 All deaths occurring during the follow up to Day 90 will be reported as an SAE. When reporting a death, the
1123 event or condition that caused or contributed to the fatal outcome should be reported as a single medical concept.
1124 AE occurring within 30 days of randomization and all SAEs will be reported in the CRF. Severity and
1125 relationship definitions are presented below.

1126 11.2. Definitions of AE-Related Terms

AE Severity	
Mild	Awareness of sign or symptom but easily tolerated
Moderate	Discomfort sufficient to cause interference with normal activities.
Severe	Incapacitating, with inability to perform normal activities.
AE Relationship	
Related	A clinical event, including laboratory test abnormality, where there is a “reasonable possibility” that the SAE was caused by the study drug, meaning that there is evidence or arguments to suggest a causal relationship.
Probably	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.
Possibly	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unrelated	This category is applicable to AEs which are judged to be clearly and incontrovertibly due to extraneous causes (diseases, environment, etc.) and do not meet the criteria for drug relationship listed for the above-mentioned conditions.

1127

1128 12. CLINICAL MANAGEMENT OF ADVERSE EVENTS

1129 12.1. Identification of Adverse Events by the Investigator

1130 AE monitoring and reporting will be followed-up until Day 30. SAEs will be followed through the final study
1131 exit visit (Day 90 Visit or death or end of study whichever is sooner) or until the subject is deemed “lost to
1132 follow-up”.

1133 AE identification while the subject is admitted to the acute stroke hospital will be collected via acute stroke
1134 hospital patient records and verbal histories from the subject or legally authorized representative (LAR). For

1135 follow up visits after discharge from the acute stroke hospital the subject (or LAR if the subject is not able to
1136 respond to the questions) will be asked about the occurrence of AEs since the last contact, and if available, from
1137 records at the acute stroke hospital. AEs that were ongoing at the last contact will be updated with a stop date or
1138 confirmed as ongoing. AE collection will continue until Day 30, and SAE to Day 90 or the final contact.

1139 A consistent methodology of eliciting AEs at all subject evaluation timepoints will be used. Non-directive
1140 questions include: How have you felt since your last clinical visit/hospital discharge? Have you had any new or
1141 changed health problems since you were last here? Have you had any unusual or unexpected worsening of your
1142 underlying medical condition or overall health? Have there been any changes in the medicines you take since
1143 your last clinical visit/hospital discharge?

1144 Diagnosis versus signs and symptoms for the purpose of AE reporting: if known at the time of reporting, a
1145 diagnosis should be reported rather than individual signs and symptoms. However, if a constellation of signs
1146 and/or symptoms cannot be medically characterized as a single diagnosis it is acceptable to report the
1147 information that is ultimately available.

1148 **12.2. Reporting of Adverse Events**

1149 AEs should be reported as they occur on the electronic Case Report Form (e-CRF). Documentation must be
1150 supported by an entry in the subject's file. Each event should be described in detail along with start and stop
1151 dates, severity, relationship to investigational product as judged by the investigator, action taken and outcome.

1152 **12.3. Reporting of Serious Adverse Events**

1153 In order to comply with current regulations on SAE reporting to health authorities, the investigator must
1154 document all SAEs regardless of causal relationship and notify the Sponsor. The Investigator will give access
1155 and provide the Sponsor with all necessary information to allow the Sponsor to conduct a detailed analysis of the
1156 safety of the investigational product. It is the responsibility of the Investigator to request all necessary
1157 documentation (e.g., medical records, discharge summary, autopsy) in order to provide comprehensive safety
1158 information. All relevant information must then be transcribed into the e-SAE Form.

1159 **12.4. Reporting by the Investigator**

1160 All SAEs must be reported to the Sponsor within 24 hours of the local Investigator's first awareness of its
1161 occurrence. SAEs will be reviewed by the trial medical monitor.

1162 The investigator will report the SAEs using the e-SAE form in the e-CRF, which will send an immediate alert to
1163 the Sponsor. If the e-CRF system is not available, a paper SAE form should be directed within 24 hours.

1164 **12.5. Reporting SAEs to the Health Authorities and Ethics Committees**

1165 The Sponsor will inform the relevant health authorities of any reportable SAEs according to the local regulatory
1166 requirements. Reporting to the health authorities will be according to the Sponsor's standard operating
1167 procedures.

1168 SAEs that are assessed by the Sponsor to be unexpected and related to study drug (expedited reporting SAEs)
1169 will be reported to the regulatory agencies as per country requirements. All other SAEs will be reported to
1170 regulatory agencies based upon local reporting requirements.

1171 The Sponsor's medical monitor or designee will notify the investigators in writing of the occurrence of any
1172 reportable SAEs. The Sponsor or delegate will be responsible for reporting suspected unexpected serious adverse
1173 reaction to any Central Ethics Committees in compliance with local current legislation. The investigators will be
1174 responsible for informing their local ethics committees of any reportable SAEs as per their local requirements.

1175

1176 **13. DATA SAFETY MONITORING BOARD**

1177 The independent Data safety monitoring board (DSMB) will be composed of an experienced neurologist, an
1178 interventionalist, and a biostatistician, which are not involved in the trial. The DSMB will meet at least once a
1179 year, and is provided with structured unmasked reports, prepared by the trial statistician, for their reference only.

1180 DSMB is responsible for recommendations to the executive committee regarding stopping or extending the trial.
1181 In addition, the DSMB will review the occurrence of SAEs and make recommendations to the executive
1182 committee regarding safety of the trial.
1183

1184 **14. IMAGING CORE LABORATORY**

1185 Centralized imaging core laboratories will be used in this trial to provide consistent assessment of all the images.
1186 CT/MR and angiographic images will be independently reviewed by two independent central imaging core
1187 laboratories respectively. CT/MR core laboratory will review CT/MR images obtained at baseline and within 24
1188 hours for confirmation of inclusion criteria, ASPECTS score, collateral circulation classification, and
1189 presence/absence of hemorrhage. Angiographic core laboratory will review angiographic images from the
1190 procedure to determine clot location and recanalization. CT/MR core laboratory will be independent from the
1191 angiographic core laboratory to ensure the CT/MR core laboratory is blinded to the treatment allocation.
1192

1193 **15. CLINICAL EVENTS COMMITTEE**

1194 The Clinical events committee (CEC) will be comprised of three expert physicians independent of the
1195 investigational sites. This committee will validate all the complications that occur over the course of the study
1196 and categorized for severity and relatedness according to the definition in the Adverse Event section in the CEC
1197 Manual of Operations. The CEC can request any additional source information and images supporting the
1198 adverse events to assist with the adjudication.
1199

1200 **16. STATISTICS**

1201 **16.1. Sample size estimates**

1202 According to the previous study data^{12,24-26}, we hypothesis that the 90-day follow-up proportion of independent
1203 functional outcome is 43% both in the primary-thrombectomy group and bridging-therapy group. The clinically
1204 relevant non-inferiority margin Δ was -10.0%. To maintain the alpha, Pocock Analog Alpha Spending Function
1205 is used. Sample size and power are computed incorporating a five-look group-sequential analysis plan with a
1206 one-sided α at 0.025, 918 cases provide 80% power for testing the primary hypothesis of this trial; assuming the
1207 attrition rate is 5% for the primary end-point, the total sample size is up to 970. The evaluable sample size is 194
1208 at each interim analysis. Therefore, in each interim analysis, 97 cases should be enrolled in each treatment group.

1209 **16.2. Analysis Populations**

1210 **16.2.1. Intention-to-treat Population**

1211 The primary efficacy analysis will be conducted in the intention-to-treat (ITT) population, defined as all subjects
1212 randomized into the trial with grouping by randomized treatment, regardless of treatment actually received.
1213 Deceased subject will be included in the ITT population with a mRS score of 6.

1214 **16.2.2. Per-Protocol Population**

1215 The primary analysis will be repeated on the Per-Protocol (PP) population, defined to be all subjects randomized
1216 and treated, with no major protocol deviations. This population will be determined via blinded review of
1217 protocol deviations at the end of the trial before database lock and unblinding. Prior to unblinding, the imaging
1218 from each subject at the time of inclusion will be adjudicated to determine whether they have met the criteria for
1219 endovascular intervention, and hence for the trial. This will include review of baseline NCCT and CTA. Subjects
1220 who do not meet the imaging criteria outlined in the trial inclusion/exclusion criteria, will not be included in the
1221 PP population.

1222 Patients who withdraw informed consent immediately after randomization and are not to receive any treatment
1223 should be excluded from all analysis populations.

1224 **16.3. Analysis of Primary Efficacy Outcome**

1225 Non-inferiority test will be used to test the primary hypothesis that the proportion of patients with independent
1226 functional outcome will be non-inferior in the primary-thrombectomy group compared to the bridging-therapy
1227 group. We desired a maximum of 5 looks when approximately 20, 40, 60, 80, and 100% of the total sample size
1228 finish the follow-up, monitoring and data cleaning processes. A group-sequential test strategy was designed to
1229 have reasonable chances of stopping as early as possible, either because of efficacy or safety reasons. The
1230 independent DSMB may recommend stopping the trial either for effectiveness, or safety in case the stopping
1231 boundaries are crossed at interim analysis. For shedding cases, follow-up will be performed until the end of the
1232 study, and the results will be included in the final analysis. Statistical analysis will be performed on the SAS 9.3
1233 system. Details of these are provided in the Statistical Analysis Plan.

1234 **16.4. Analysis of secondary efficacy outcomes**

1235 The key secondary outcomes will be tested in the following order:

- 1236 1.The Proportion of mRS score 0 to 1 at 90 days;
- 1237 2.Shift in the distribution of mRS scores at 90 days in EVT alone versus rt-PA plus EVT (ordinal shift analysis);
- 1238 3.Successful recanalization proportion immediate after EVT.
- 1239 4.Vessel recanalization rate evaluated by CTA or MRA within 48 hours;
- 1240 5.The change of the National Institutes of Health Stroke Scale (NIHSS) score at 24 hours from baseline;
- 1241 6.The change of the NIHSS score at 5-7 days or discharge if earlier from baseline;
- 1242 7.European Quality Five-Dimension Five-Level (EQ-5D-5L) scale score at 90 days.

1243 **16.5. Adjustment for covariates and subgroup analyses**

1244 In addition to the primary and secondary analyses adjusting for age, sex, baseline NIHSS score, baseline
1245 ASPECTS score, occlusion location, exploratory analyses will be conducted to determine the potential roles of
1246 common baseline characteristics and assess potential heterogeneity of treatment effect across subgroups. Specific
1247 subgroups of interest include the age ≥ 70 vs. < 70 years old, male vs. female, subject with different baseline
1248 stroke severity (on NIHSS and measured radiologically on ASPECTS), baseline occlusion location (ICA
1249 occlusion: no vs. yes), cause of stroke, onset to randomization time. Full details will be specified in detail in the
1250 Statistical Analysis Plan.

1251 **16.6. Handling of Missing Data**

1252 Every effort will be made to keep missing data, particularly the Day 90 outcome assessments, to a minimum.
1253 However, some missing data may be inevitable due to, for example, loss to follow-up. Deceased subject will
1254 score 6 on the mRS and be counted as non-responders. For the primary analysis for regulatory submission, we
1255 will assume that subject missing the primary endpoint data will be considered to be non-responders. Sensitivity
1256 analyses using various imputation techniques will be specified prospectively in the Statistical Analysis Plan
1257 before the database lock for the interim analysis if more than 5% of subject randomized are missing the primary
1258 endpoint.

1259 **16.7. Analyses of Safety**

1260 The main analyses will be frequency of sICH and 90-day mortality. It is expected that the safety population and
1261 the ITT population will be near-identical. Full details will be specified in detail in the Statistical Analysis Plan.

1262 **16.8. SAEs**

1263 SAEs over the 90-day study period will be summarized by presenting, for each treatment group, the number and
1264 percentage of subjects having at least one SAE, having an SAE in each body system and preferred term, by
1265 severity and relatedness to study medication. The frequencies and incidences of SAEs occurring in subjects in
1266 the active and control groups will be summarized within treatment group by the Medical Dictionary for
1267 Regulatory Activities (MedDRA) System Organ Class (SOC). The frequencies and incidences of SAEs and
1268 discontinuations due to SAEs occurring in subjects in the active and control groups will be summarized within
1269 treatment group.

1270 16.9. AEs

1271 Additional analyses will consider the frequency of AEs and discontinuations due to AEs. AEs will be
1272 summarized by presenting, for each treatment group, the number and percentage of subjects having any AE,
1273 having an AE in each body system and preferred term. Severity and relatedness to study medication will be
1274 recorded. The frequencies and incidences of AEs occurring in subjects in the active and control groups will be
1275 summarized within treatment group by the Medical Dictionary for Regulatory Activities (MedDRA) System
1276 Organ Class (SOC).

1277

1278 17. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

1279 The sponsor or delegate will be permitted to visit the study facilities at any reasonable time in order to maintain
1280 current, detailed knowledge of the study through review of the records, source documents, observation, and
1281 discussion of the conduct and progress of the study. In addition, the sponsor will maintain regular telephone and
1282 written communication with all investigators through the coordinating center. The sponsor (or delegate) will be
1283 given complete access to all components of the study facility that pertain to the conduct of this study, and may be
1284 present to observe any aspect of the conduct of the study by medical and paramedical staff, including but not
1285 limited to drug preparations, dosing, sample collections, and clinical observations. E-CRFs will be monitored
1286 with sufficient frequency to assess the following: Subject randomization, compliance with protocol procedures,
1287 the completeness and accuracy of data entered into the e-CRFs, verification of e-CRF data against original
1288 source documents, and occurrence of AEs. Adequate time and all documents for these monitoring visits must be
1289 made available by the investigators. The investigators will permit trial-related monitoring, audits, REB/IRB
1290 review, and regulatory inspections, providing direct access to source data/documents.

1291

1292 18. QUALITY CONTROL AND QUALITY ASSURANCE

1293 To ensure monitoring responsibilities are performed to the fullest extent possible, industry experienced study
1294 monitors will perform on site data verification for the trial. All data monitored on site are verified for accuracy
1295 and completeness using source documents for all subjects. In addition, 100% of subjects enrolled are monitored
1296 for the presence of signed consent.

1297 Monitoring of the investigational sites will be conducted by the sponsor or contracted to a qualified clinical
1298 research organization. The sponsor will determine the extent, nature, and frequency of on-site visits that are
1299 needed to ensure that the study is being conducted in accordance with the approved protocol (and any
1300 amendments), Good Clinical Practice (GCP), and all applicable regulatory requirements. At site visits, the
1301 monitor will, as required, assess the progress of the study; check that the study data chosen for verification are
1302 authentic, accurate, and complete; verify that the safety and rights of patients are being protected; compare
1303 original documents with data entered into the study database; and identify any issues and address their
1304 resolution.

1305 The investigator agrees to allow the monitor(s) direct access to all relevant documents, and to allocate his/her
1306 time and the time of staff to discuss findings, corrective actions and any relevant issues. In addition to contacts
1307 during the study, the monitor may also contact the site prior to the start of the study to discuss the protocol and
1308 data collection procedures with site personnel.

1309 Additional on-site monitoring verification includes: ongoing evaluation of the adequacy of site facilities and staff,
1310 site recruitment, subject randomization, the presence of regulatory documents, and specific review of documents
1311 and data. The initial performance-monitoring visit to a site takes place after the initial subject(s) are enrolled and
1312 will continue according to enrolment for the duration of the trial.

1313 During the monitoring visit, any omissions and corrections to data submitted to the database will be noted and
1314 queries will be generated by the monitor and resolved by the site.

1315 The close-out monitoring visit by the monitor will take place at the completion of subject enrollment and
1316 protocol required follow-up visits at the performance site. At that visit, the monitor will again review the
1317 presence of a regulatory file and verify documents for currency and completion as directed by the clinical
1318 research unit. Sites will be instructed in the record retention of all trial documents. Principal Investigators are
1319 directed to close the trial and issue a final report to the institutional review board. Finally, any additional special
1320 considerations for the auditing of any additional safety issues are made during this final monitoring visit.

1321 Except for an emergency situation in which proper care for the protection, safety and well- being of the study
1322 subjects requires medical treatment, the study will be conducted as described in the approved protocol,
1323 International Conference on Harmonization-Good Clinical Practice (ICH-GCP), Standard Operating Procedures
1324 (SOPs) and regulatory requirements. All medical treatments will be recorded. Any deviation(s) from the protocol
1325 will be recorded and presented in the final clinical study report.

1326 **18.1. Audits and Inspections**

1327 In accordance with the principles of ICH-GCP, the study site may be inspected by regulatory authorities. Quality
1328 Assurance (QA) or their designates. The investigator and relevant clinical support staff will be required to be
1329 actively involved in audits and inspections, including staff interviews, and to make all necessary documentation
1330 and data available upon request.

1331 During the course of the study and/or after it has been completed, one or more investigator site audits may be
1332 undertaken by auditors. The purpose of these audits is to determine whether or not the study is being/has been
1333 conducted and monitored in compliance with recognized ICH-GCP, protocol and approved amendment
1334 requirements, applicable local SOPs, and local laws and regulations. It is the responsibility of the investigator
1335 and site staff to promptly address any deficiencies stemming out of regulatory inspections and delegate audits,
1336 and to ensure that agreed-upon corrective and preventive actions are implemented as soon as possible.

1337 An inspection by any regulatory authority may occur at any time during or after completion of the study.

1338 **18.2. Protocol Amendments and Revisions**

1339 Should amendments and/or revisions to the protocol be required, they will be originated and documented by the
1340 sponsor. All amendments and/or revisions will be made in compliance with sponsor SOPs. All amendments will
1341 be submitted to the research ethics board/Institutional Review Board (REB/IRB) for approval prior to
1342 implementation. It is the sponsor's responsibility to submit all revisions and amendments to regulatory
1343 authorities when necessary.

1344

1345 **19. ETHICAL CONSIDERATION**

1346 This research followed the ethical principles of the Helsinki Declaration. This protocol and the consent forms
1347 will be submitted to each hospital's REB/IRB. Before initiation of the study, a copy of the REB/IRBs' approval
1348 letters will be provided to the sponsor and the membership list of the REB/IRB will be kept on file. To make
1349 sure the subjects fully understand about this trial, the investigators must provide the patients or their legal
1350 representatives with detailed information about the clinical trial, including the purpose of the trial, possible
1351 benefits and risks, and the rights/obligations. Subjects have the right to withdraw from the study at any time if
1352 they wish to do so. The privacy protection of subjects has to be ensured. The patients or their legal
1353 representatives give their written informed consent prior to the study. Each patient must leave contact
1354 information to the investigator of the participating center. At the same time, the investigator must leave his own
1355 phone number to the patient so that the patient can find the investigator at any time. Ethical approval for the
1356 study was obtained by the Ethics Committee of the participating centers. SAEs will be reported to the REB/IRB
1357 according to their requirements.

1358

1359 **20. DATA HANDLING AND RECORD KEEPING**

1360 20.1. Data Handling

1361 During the trial, clinical data reported in the e-CRFs will be integrated into the clinical database under the
1362 responsibility of the Sponsor or their qualified representative. Quality control in the form of computerized logic
1363 and/or consistency checks will be systematically applied in order to detect errors or omissions. In addition, safety
1364 reviews may be performed several times by the Sponsor's staff in the course of the trial. Any questions
1365 pertaining to the reported clinical data will be submitted to the investigator for resolution. Each step of this
1366 process will be monitored through the implementation of individual passwords to maintain appropriate database
1367 access and to ensure database integrity.

1368 After integration of all corrections in the complete set of data, the database will be released for statistical
1369 analysis.

1370 20.2. Investigator Files/Retention of Documents

1371 The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully
1372 documented and the study data to be subsequently verified. These documents should be classified into two
1373 different separate categories: Investigator's Study File; and Subject Clinical Source Documents.

1374 The Investigator's Study File will contain the Protocol/Amendments, CRFs, REB/IRB and governmental
1375 approval with correspondence, all versions of ethics approved informed consent forms, staff curriculum vitae
1376 and authorization forms and other appropriate documents/correspondence, etc.

1377 Subject clinical source documents (usually defined by the project in advance to record efficacy/safety parameters
1378 independent of the CRFs) would include subject hospital/clinic records, physician's and nurse's notes,
1379 appointment book, original laboratory reports, ECG, image data, signed consent forms, consultant letters, and
1380 source worksheets. The investigator must keep these two categories of documents on file according to local
1381 clinical trial regulation.

1382 The Investigator and the sponsor will maintain the records of disposition of the drug and the clinic records in
1383 accordance with ICH-GCP and each applicable regulatory agency. Clinic records will be retained at the site until
1384 informed by the sponsor to destroy the documents. If the clinical study must be terminated for any reason, the
1385 investigator will return all study materials to the sponsor and provide a written statement as to why the
1386 termination has taken place and notify the REB/IRB.

1387 20.3. Source Documents and Background Data

1388 Any investigators shall supply the sponsor, upon request, with any required background data from the study
1389 documentation or clinic records. This is particularly important when e-CRFs are illegible or when errors in data
1390 transcription are suspected. In case of special problems and/or governmental queries or requests for audit
1391 inspections, it is also necessary to have access to the complete study records, provided that subject
1392 confidentiality is protected.

1393 20.4. Case Report Forms

1394 For each subject randomized, an e-CRF must be completed and signed by the investigator. If a subject withdraws
1395 from the study, the reason must be noted on the CRF. All forms should be completed within five business days
1396 of subject visit. All corrections will be tracked in the e-CRF audit trail. The Investigator should ensure the
1397 accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all
1398 required reports.

1399 20.5. Confidentiality

1400 All imaging, evaluation forms, reports, and other records that leave the site are identified only by the site and
1401 subject number to maintain subject confidentiality. All records are kept in a locked file cabinet. Clinical
1402 information is not released without written permission of the subject, except as necessary for monitoring by
1403 REB/IRB, health authorities, the sponsor, or the sponsor's designee.

1404 All study investigators at the clinical sites must ensure that the confidentiality of personal identity and all
1405 personal medical information of study subjects are maintained at all times. clinical sites must conform to local
1406 privacy and confidentiality law and custom. On the CRFs and other study documents or image materials
1407 submitted to the CRU, the subjects are identified only by study identification codes.

1408 Personal medical information may be reviewed for the purpose of verifying data recorded in the CRF by the site
1409 monitors. Other properly authorized persons, such as the regulatory authorities, may also have access to these
1410 records. Personal medical information is always treated as confidential.

1411

1412 **21. PUBLICATION AND PRESENTATION POLICY**

1413 A trial executive committee shall be formed, and include at least the trial principal investigator and co-principal
1414 investigator, the statistical consultant, and representatives of the Sponsor. The trial executive committee will be
1415 co-authors on all publications and presentations. The primary author list for the primary publication will consist
1416 of the executive committee and the site principal/qualified investigator at each of the sites. A formal publication
1417 policy will be presented and developed by the trial executive.

1418

1419 **22. DATA-SHARING PLAN**

1420 The sponsor will permit any and all academic publications arising from the trial data provided that no publication
1421 containing unblinded trial data precedes publication of the overall trial results in a peer-review journal, and are
1422 (1) approved by the trial executive committee and (2) the publication authors notify the sponsor at least 30 days
1423 prior to submittal for publication with a copy of such proposed publication for the sponsor's review and
1424 comment. Employees or consultants of the sponsor will only be named as authors in any such publication if the
1425 parties agree that it is appropriate under the usual conventions used by academic institutions for naming authors
1426 in scientific publications. Upon request of the sponsor the publication or disclosure shall be delayed for up to 60
1427 days in order to allow for the filing of a patent application. The Executive Committee will make the trial results
1428 available as free-access using PubMed and on Chinese Clinical Trials Registry. (www.chictr.org.cn).

1429

1430 **23. STUDY ORGANIZATION AND FUNDING**

1431 DEVT trial is an investigator-initiated study which is organized by the second affiliated hospital of the Third
1432 Military Medical University and conducted in about 30 comprehensive stroke centers in China. The authors
1433 disclosed receipt of the following financial support: (1) National Natural Science Foundation of China (Nos.
1434 81525008, 81901236, 81801157), (2) Chongqing Major Disease Prevention and Control Technology Research
1435 Project (No. 2019ZX001), (3) Major clinical innovation technology project of the Second Affiliated Hospital of
1436 the Army Military Medical University (No. 2018JSLC0017), and (4) Clinical Medical Research Talent Training
1437 Program of Army Medical University (2019XLC2008, 2019XLC3016). The funders had no involvement in the
1438 study design, data collection, analysis and interpretation, writing or decision to submit the paper.

1439

1440 Appendix 1 - Classification of Subtype of Acute Ischemic Stroke

1441 The TOAST classification system includes five categories: 1) large-artery atherosclerosis, 2) cardioembolism, 3)
1442 small-artery occlusion (lacunae), 4) stroke of other determined etiology, and 5) stroke of undetermined etiology
1443 (Table 1)²⁷. Diagnoses are based on clinical features and on data collected by tests such as brain imaging
1444 (CT/MRI), cardiac imaging (echocardiography, etc.), duplex imaging of extracranial arteries, arteriography, and
1445 laboratory assessments for a pro-thrombotic state.

1446 The physician can apply the clinical and imaging findings when first assessing the patient and then consider the
1447 results of other diagnostic tests later. An important part of the classification is the ability of the physician to
1448 categorize a specific subtype diagnosis as probable or possible based on the degree of certainty. A "probable"
1449 diagnosis is made if the clinical findings, neuroimaging data, and results of diagnostic studies are consistent with
1450 one subtype and other etiologies have been excluded. A "possible" diagnosis is made when the clinical findings
1451 and neuroimaging data suggest a specific subtype but other studies are not done. Because many patients will
1452 have a limited number of diagnostic tests, the probable and possible subcategorizations allow the physician to
1453 make as precise a subgroup diagnosis as can be achieved.

1454 Large artery atherosclerosis

1455 These patients will have clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of
1456 a major brain artery or branch cortical artery, presumably due to atherosclerosis (Table 2). Clinical findings
1457 include those of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem
1458 or cerebellar dysfunction. A history of intermittent claudication, transient ischemic attacks (TIAs) in the same
1459 vascular territory, a carotid bruit, or diminished pulses helps support the clinical diagnosis. Cortical or cerebellar
1460 lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter on CT or MRI are
1461 considered to be of potential large-artery atherosclerotic origin. Supportive evidence by duplex imaging or
1462 arteriography of a stenosis of greater than 50% of an appropriate intracranial or extracranial artery is needed.
1463 Diagnostic studies should exclude potential sources of cardiogenic embolism. The diagnosis of stroke secondary
1464 to large artery atherosclerosis cannot be made if duplex or arteriographic studies are normal or show only
1465 minimal changes.

1466 Cardioembolism

1467 This category includes patients with arterial occlusions presumably due to an embolus arising in the heart (Table
1468 2). Cardiac sources are divided into high-risk and medium-risk groups based on the evidence of their relative
1469 propensities for embolism (Table 3). At least one cardiac source for an embolus must be identified for a possible
1470 or probable diagnosis of cardioembolic stroke. Clinical and brain imaging findings are similar to those described
1471 for large-artery atherosclerosis. Evidence of a previous TIA or stroke in more than one vascular territory or
1472 systemic embolism supports a clinical diagnosis of cardiogenic stroke. Potential large-artery atherosclerotic
1473 sources of thrombosis or embolism should be eliminated. A stroke in a patient with a medium-risk cardiac source
1474 of embolism and no other cause of stroke is classified as a possible cardioembolic stroke.

1475 Small artery occlusion (lacunae)

1476 This category includes patients whose strokes are often labeled as lacunar infarcts in other classifications (Table
1477 2). The patient should have one of the traditional clinical lacunar syndromes and should not have evidence of
1478 cerebral cortical dysfunction. A history of diabetes mellitus or hypertension supports the clinical diagnosis. The
1479 patient should also have a normal CT/MRI examination or a relevant brain stem or subcortical hemispheric
1480 lesion with a diameter of less than 1.5cm demonstrated. Potential cardiac sources for embolism should be absent,
1481 and evaluation of the large extracranial arteries should not demonstrate a stenosis of greater than 50% in an
1482 ipsilateral artery.

1483 Acute stroke of other determined etiology

1484 This category includes patients with rare causes of stroke, such as nonatherosclerotic vasculopathies,
 1485 hypercoagulable states, or hematologic disorders. Patients in this group should have clinical and CT or MRI
 1486 findings of an acute ischemic stroke, regardless of the size or location. Diagnostic studies such as blood tests or
 1487 arteriography should reveal one of these unusual causes of stroke. Cardiac sources of embolism and large-artery
 1488 atherosclerosis should be excluded by other studies.

1489 **Stroke of undetermined etiology**

1490 In several instances, the cause of a stroke cannot be determined with any degree of confidence. Some patients
 1491 will have no likely etiology determined despite an extensive evaluation. In others, no cause is found but the
 1492 evaluation was cursory. This category also includes patients with two or more potential causes of stroke so that
 1493 the physician is unable to make a final diagnosis. For example, a patient with a medium-risk cardiac source of
 1494 embolism who also has another possible cause of stroke identified would be classified as having a stroke of
 1495 undetermined etiology. Other examples would be a patient who has atrial fibrillation and an ipsilateral stenosis
 1496 of 50%, or the patient with a traditional lacunar syndrome and an ipsilateral carotid stenosis of 50%.

1497

1498 **Table 1. TOAST Classification of Subtypes of Acute Ischemic Stroke**

Large artery atherosclerosis (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacunae)*
Stroke of other determined etiology*
Stroke of undetermined etiology
a. Two or more causes identified
b. Negative evaluation
c. Incomplete evaluation

1499 TOAST denotes Trial of Org 10172 in Acute Stroke Treatment.

1500 *Possible or probable depending on results of ancillary studies.

1501

1502 **Table 2. Features of TOAST Classification of Subtypes of Ischemic Stroke**

Features	Subtype				Other cause
	Large artery atherosclerosis	Cardioembolism	Small artery occlusion (lacunae)		
Clinical					
Cortical or cerebellar dysfunction	+	+	-		+/-
Lacunar syndrome	-	-	+		+/-
Imaging					
Cortical, cerebellar, brain stem, or subcortical infarct > 1.5 cm	+	+	-		+/-

Subcortical or brain stem infarct < 1.5 cm	-	-	+/-	+/-
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Tests

Stenosis of extracranial internal carotid artery	+	-	-	-
Cardiac source of emboli	-	+	-	-
Other abnormality on tests	-	-	-	+

1503

1504

Table 3. TOAST Classification of High- and Medium-Risk Sources of Cardioembolism**High-risk sources**

Mechanical prosthetic valve
 Mitral stenosis with atrial fibrillation
 Atrial fibrillation (other than lone atrial fibrillation)
 Left atrial/atrial appendage thrombus
 Sick sinus syndrome
 Recent myocardial infarction (<4 weeks)
 Left ventricular thrombus
 Dilated cardiomyopathy
 Akinetic left ventricular segment
 Atrial myxoma
 Infective endocarditis

Medium-risk sources

Mitral valve prolapse
 Mitral annulus calcification
 Mitral stenosis without atrial fibrillation
 Left atrial turbulence (smoke)
 Atrial septal aneurysm
 Patent foramen ovale
 Atrial flutter
 Lone atrial fibrillation
 Bioprosthetic cardiac valve
 Nonbacterial thrombotic endocarditis
 Congestive heart failure
 Hypokinetic left ventricular segment
 Myocardial infarction (> 4 weeks, < 6 months)

1505

1506 Appendix 2 - ASITN/SIR Collateral Vessel Grading System

1507 Collateral vessel status was evaluated by using the American Society of Interventional and Therapeutic
1508 Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral vessel grading system²⁸. Collateral
1509 vessel scores are categorized into ASITN/SIR grades 0 or 1, 2, and 3 or 4. The following scoring system
1510 provides a guide.

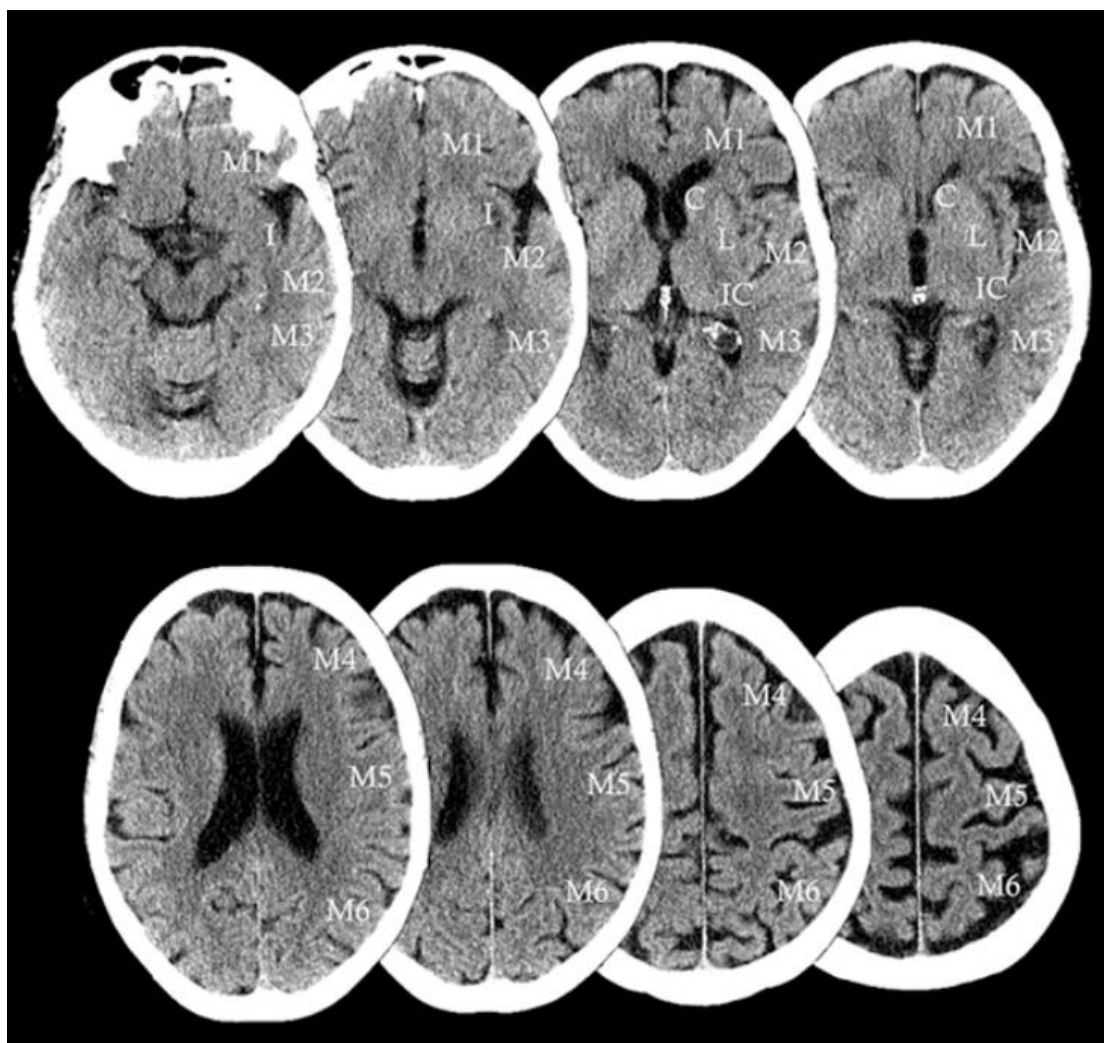
Grade	Description
0	No collateral vessels visible to the ischemic site
1	Slow collateral vessels to the periphery of the ischemic site with persistence of some of the defect
2	Rapid collateral vessels to periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory
3	Collateral vessels with slow but complete angiographic blood flow of the ischemic bed by the late venous phase
4	Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion

1511

1512

1513 Appendix 3 - The Alberta Stroke Program Early Computed Tomography Score (ASPECTS)

1514 NCCT shall be scored using ASPECTS, a 10-point score derived by examining each of 10 regions on the middle
1515 cerebral artery territory²⁹. Ischemic change present is scored as 0; ischemic change absent is score as 1. Adding
1516 up the score gives a maximum of 10 (favorable scan) and minimum of 0 (unfavorable scan). The score is highly
1517 reliable when trichotomized into 0-4 (severe ischemic change, large core), 5-7 (moderate ischemic change) and
1518 8-10 (minimal ischemic change, small core). ASPECTS may be less reliable early in stroke (i.e. within 90
1519 minutes of onset); however, at later time windows it should be easy to recognize large areas of irreversible
1520 damage. Having a good quality scan and optimization of scanner is key to successful interpretation. Further
1521 information is available at: ww.aspectsinstroke.com.



1522

1523

1524 **Appendix 4 - Modified Rankin Scale (MRS)**

Grade	Description ³⁰
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Death

1525

1526

1527 Appendix 5 - Expanded Thrombolysis In Cerebral Infarction (eTICI) Scale

Score	Description ¹⁸
0	No perfusion or antegrade flow beyond site of occlusion
1	Penetration but not perfusion. Contrast penetration exists past the initial obstruction but with minimal filling of the normal territory
2	Incomplete perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but rate of entry or clearance from the bed is slower or incomplete when compared with non-involved territories
2a	Some perfusion with distal branch filling of < 50% of territory visualized
2b	Substantial perfusion with distal branch filling of \geq 50% of territory visualized
2c	Near-complete perfusion except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli
3	Complete perfusion with normal filling of all distal branches

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1531 Investigator's Agreement

1532 I have read the attached protocol: a randomized, controlled, multicenter trial of Direct Endovascular treatment
1533 Versus standard bridging Therapy for acute stroke patients with large vessel occlusion in the anterior circulation
1534 (DEVT Trial), Version 2.0 dated 1st August 2019 and agree to abide by all provisions set forth therein. I agree to
1535 comply with the current International Conference on Harmonization Guidelines for Good Clinical Practice and
1536 the laws, rules, regulations and guidelines of the community, country, state or locality relating to the conduct of
1537 the clinical study. I also agree that persons debarred from conducting or working on clinical studies by any court
1538 or regulatory agency will not be allowed to conduct or work on studies for the sponsor.

1539

1540

1541

1542

1543

1544 Name Site Principal Investigator

Signature

1545

1546

1547 Name of Clinical Site

Date

1548

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Summary of Changes - Protocol DEVT Version 1.0 to Version 2.0

Below is the table of changes. Deleted items are identified with Strikethrough font. Additional wording is in bold font

Section(s)	Protocol Version 1.0 Change From:	Protocol Version 2.0 Change To:	Rationale
List of Abbreviations		MedDRA-Medical Dictionary for Regulatory Activities SOC-System Organ Class	Addition
Schedule of Assessments	Weight	Weight* *The subject's actual weight will be measured in hospital using standard hospital scales (i.e., stand up or in-bed scales if the subject is not ambulatory). If actual weight cannot be measured for any reason (due to, for example severe illness or unavailability of in-bed scales at the site), weight will be determined by first asking the subject, second asking a family member or third by estimation.	Clarification
Schedule of Assessments	Prior medications Concomitant medications	Prior medications [§] Concomitant medications [§] §Prior and concomitant medications will be listed per patient, with the listings separated within treatment group.	Clarification
Study Synopsis - Assessment of Efficacy & Section 8.2 Secondary Efficacy Outcomes	Successful recanalization proportion immediate after EVT. Successful recanalization is defined as a modified Treatment in Cerebral Infarction score of 2b (50 to 99% reperfusion) or 3 (complete reperfusion) in the post-procedure angiography	Successful recanalization proportion immediate after EVT. Successful recanalization is defined as a expanded Thrombolysis In Cerebral Infarction score of 2b (substantial perfusion), 2c (near-complete perfusion) or 3 (complete reperfusion) in the post-procedure angiography	Updated definition, in response to a comment received from the Research Committee
Section 1 BACKGROUND INFORMATION		In addition, IVT before EVT is associated with an increased incidence of clot migration, resulting in an	Addition

		<p>increased rate of clots inaccessibility by mechanical thrombectomy. [reference: <i>Stroke</i> 2017;48:2450-6.]</p> <p>Another meta-analysis showed that direct endovascular treatment may carries comparable effectiveness and safety as compared with bridging therapy by pooling studies with lower selection bias. [reference: <i>Journal of neurointerventional surgery</i> 2019;11:20-7.]</p>	
Section 10.1 The Modified Rankin Scale	Premorbid mRS status will also be obtained retrospectively at 24 Hours	Premorbid mRS status will also be obtained retrospectively and reported on the 24h CRF page.	Clarification of the premorbid mRS collection time and reporting on the CRF
Section 16.8 SAEs		<p>SAEs over the 90-day study period will be summarized by presenting, for each treatment group, the number and percentage of subjects having at least one SAE, having an SAE in each body system and preferred term, by severity and relatedness to study medication. The frequencies and incidences of SAEs occurring in subjects in the active and control groups will be summarized within treatment group by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC). The frequencies and incidences of SAEs and discontinuations due to SAEs occurring in subjects in the active and control groups will be summarized within treatment group</p>	<p>Addition, To be consistent with the Statistical Analysis Plan</p>
Section 16.9 AEs		<p>Additional analyses will consider the frequency of AEs and discontinuations due to AEs. AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each body system and preferred term. Severity and</p>	<p>Addition, To be consistent with the Statistical Analysis Plan</p>

		<p>relatedness to study medication will be recorded. The frequencies and incidences of AEs occurring in subjects in the active and control groups will be summarized within treatment group by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC).</p>	
<p>Section 23. STUDY ORGANIZATION AND FUNDING</p>	<p>DEVT trial is an investigator-initiated study which is organized by the second affiliated hospital of the Third Military Medical University and conducted in about 30 comprehensive stroke centers in China. The authors disclosed receipt of the following financial support: (1) National Science Fund for Distinguished Young Scholars (No. 81525008), and (2) Major clinical innovation technology project of the Second Affiliated Hospital of the Army Military Medical University (No. 2018JSLC0017). The funders had no involvement in the study design, data collection, analysis and interpretation, writing or decision to submit the paper.</p>	<p>DEVT trial is an investigator-initiated study which is organized by the second affiliated hospital of the Third Military Medical University and conducted in about 30 comprehensive stroke centers in China. The authors disclosed receipt of the following financial support: (1) National Natural Science Foundation of China (Nos. 81525008, 81901236, 81801157), (2) Chongqing Major Disease Prevention and Control Technology Research Project (No. 2019ZX001), (3) Major clinical innovation technology project of the Second Affiliated Hospital of the Army Military Medical University (No. 2018JSLC0017), and (4) Clinical Medical Research Talent Training Program of Army Medical University (2019XLC2008, 2019XLC3016). The funders had no involvement in the study design, data collection, analysis and interpretation, writing or decision to submit the paper.</p>	<p>Addition</p>
<p>Appendix 5 - Modified Treatment In Cerebral Infarction (mTICI) Score</p>	<p>Modified Treatment In Cerebral Infarction (mTICI) Score</p>	<p>Expanded Thrombolysis in Cerebral Infarction Scale</p>	<p>Updated definition, in response to a comment received from the Research Committee</p>