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CASSISS TRIAL PROTOCOL

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THE CASSISS TRIAL

China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A prospective, multi-center, randomized controlled trial

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The CASSISS Trial

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Full Title	China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A prospective, multi-center, randomized controlled trial (RCT)
Short Title	The CASSISS Trial
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19 **Protocol signature sheet****Name****Signature****Date**

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107 **1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

108

AE	Adverse Event
AHA	American Heart Association
ALT	Alanine transaminase
APTT	Activated Partial Thromboplastin Time
ASA	American Stroke Association
ASITN/SIR	American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading System
AST	Aspartate aminotransferase
ATM	Atmosphere
BA	Basilar Artery
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
DSMB	Data Safety and Monitoring Board
DWI	Diffusion-weighted Imaging
ECG	Electrocardiogram
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
Cr	Creatine
CRF	Case Report Form
CRP	C-reactive protein
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTP	Computed Tomography Perfusion
DSA	Digital Subtraction Angiography
DAPT	Dural Anti-Platelet Therapy
DWI	Diffusion-Weighted Imaging
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
EDC	Electronic Data Capture

FAS	Full Analysis Set
FBG	Fasting blood glucose
FIB	Fibrinogen
GCP	Good Clinical Practice
HDL	High-density Lipoprotein
HbA1c	Glycated Hemoglobin
ICA	Internal Carotid Artery
ICAS	IntraCranial Atherosclerotic Stenosis
ICF	Informed Consent Form
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention To Treat
IVRS	Interactive Voice Response System
LDL	Low-density Lipoprotein
LOCF	Last Observed Carried Forward
MCA	Middle Cerebral Artery
MRA	Magnetic Resonance Angiography
mRS	Modified Rankin Scales
MTT	Mean Transit Time
NIHSS	National Institute of Health Stroke Scale
PI	Principle Investigator
PPS	Per-Protocol Set
PT	Prothrombin Time
PWI	Perfusion Weighted Imaging
RCT	Randomized Control Trial
PTAS	Percutaneous Transluminal Angioplasty and Stenting
SAE	Serious Adverse Event
SIT	Stroke In the Territory of symptomatic intracranial stenosis
Sponsor	The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding

for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.

TC	Total Cholesterol
TCD	TransCranial Doppler
TIA	Transient Ischemic Attack
TICI	Thrombolysis in Cerebral Infarction
TT	Thrombin Time
TTP	Time-to-Peak
USA	United States of America
VA	Vertebral Artery

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111 **2. SUMMARY**

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Title	China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A prospective, multi-center, randomized controlled trial
Objectives	To determine whether intracranial angioplasty and stenting with Gateway-Wingspan stent system adds benefit to medical therapy alone for preventing the primary outcome (stroke or death within 30 days after enrollment, or stroke in the territory of the symptomatic intracranial artery between 30 days through 1 year in patients with recent TIA or stroke caused by 70% to 99% stenosis of a major intracranial artery).
Patient population	Patients with recent TIA or stroke caused by 70% to 99% stenosis of a major intracranial artery.
Sample size	380 (ratio 1:1)
Intervention	Random 1:1 allocation to medical therapy alone versus medical therapy plus intracranial angioplasty and stenting with Gateway-Wingspan stent system. Superiority is prospectively defined if the stenting arm has a significantly lower stroke or death rate.
Study design	Prospective, open-label, multi-center, randomized controlled study.
Main parameters / Outcomes	<p>Primary outcomes:</p> <ul style="list-style-type: none"> • Stroke or death within 30 days after enrollment; • Stroke in the territory of the symptomatic intracranial artery (SIT) between 30 days and 1 year <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Disabling stroke or death beyond 30 days through 3 years in both arms; • Complication rates associated with stenting procedures; • Restenosis (>50%) related to stenting within a follow-up of 3 years; • Any stroke, severe TIA, or cardiovascular events within a

	<p>follow-up of 3 years;</p> <ul style="list-style-type: none"> • National Institutes of Health Stroke Scale (NIHSS), mRS, and Barthel index assessment within a follow-up of 3 years; • The compliance rate of patients with regular medical therapy within a follow-up of 3 years; • Death rate in both arms within a follow-up of 3 years.
Follow-up schedule	Baseline, 30-day, 1-year, 2-year, and 3-year
Statistical analysis plan	<ul style="list-style-type: none"> • The primary and secondary outcomes are compared between the groups using log-rank test by ITT. • An independent groups t-test or Wilcoxon rank test are used to compare the quantitative data between the groups. • Chi-square test or Fisher exact probability method is used for categorical data between the groups. • Kaplan-Meier curves is used to show the incidence of outcomes over time. • All statistical tests are performed by two-sided test. P-value less than 0.05 is considered as statistically significant. • All the analyses are performed with the use of SAS software (SAS Institute).

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122 **3. INTRODUCTION AND RATIONALE**

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124 **3.1 Description of the disease**

125 Stroke is one of the leading causes of death in China and confers a large
126 burden and effort upon patients and health professionals.¹⁻³ In contrast to
127 Western countries, intracranial atherosclerotic stenosis (ICAS) is the most
128 common vascular lesion in patients with cerebrovascular disease, and is an
129 important cause of ischemic stroke and future recurrent events in China.⁴⁻⁷
130 Patients with ICAS have long been considered to be at high risk of recurrent
131 stroke, which led to the development and wide use of percutaneous
132 transluminal angioplasty and stenting (PTAS).⁸⁻¹²

133

134 **3.2 Description of the intervention**

135 In 2005, the Wingspan Stent system (Stryker Neurovascular, Fremont, CA,
136 USA) was approved under a Humanitarian Device Exemption by the US Food
137 and Drug Administration (FDA), and had been used to reduce the rate of
138 recurrent ischemic events among patients with severe symptomatic ICAS.¹³⁻¹⁷
139 However, the Stenting and Aggressive Medical Management for Preventing
140 Recurrent Stroke in Intracranial Stenosis trial (SAMMPRIS trial,
141 ClinicalTrials.gov number, NCT00576693), as the first RCT,¹⁸ demonstrated
142 that aggressive medical management was superior to PTAS with the
143 Wingspan stent among patients with symptomatic severe ICAS, both because
144 the risk of early stroke after stenting was high (14.7%) and because the risk of
145 stroke with aggressive medical therapy alone was lower than expected
146 (5.8%).¹⁹

147

148 **3.3 Relevance for clinical practice**

149 Since the SAMMPRIS trial, concerns have emerged that outcomes seen in a
150 clinical trial setting may not be reproducible in non-RCT setting because of
151 demonstrated more optimal surgical outcomes, less complication rates in
152 high-volume centers, and good patient selection. The technical procedural
153 problem rate, including guidewire- or angioplasty-related hemorrhage, could
154 be minimized as more experienced operators overcome the learning curve for
155 mastering the safety precautions of Wingspan stenting for ICAS.²⁰⁻²² In the
156 post-SAMMPRIS era, several single or multi-center, registration studies in
157 China,²³⁻²⁶ suggested lower risks of intracranial stenting for ICAS than those
158 reported for SAMMPRIS.¹⁹

159 Second, poor patient selection may increase the peri-operative risks and bias
160 the outcome favoring medical treatment. In the stenting arm of the
161 SAMMPRIS trial, more than 50% (115/224) of patients had a time interval

162 from qualifying event to randomization of less than 7 days.¹⁹ Short interval or
163 early stenting intervention may confer a higher risk of cerebral vascular event,
164 including thromboembolic events, perforator stroke,²⁷ or even hemorrhagic
165 transformation. Also, in the SAMMPRIS trial, 22.8% of recruited patients had
166 perforators stroke only, and those patients may not benefit from stenting in
167 addition to medical therapy. Ideally, stenting may be considered for eligible
168 patients based on poor collaterals and medical futility.²⁸

169 Third, intracranial stenting involves a trade-off between a higher short-term
170 perioperative risk in exchange for a lower long-term risk of stroke. In the
171 SAMMPRIS trial the stenting group, mostly due to periprocedural complication,
172 had more disabling or fatal stroke within 30 days than that in medical group
173 (7.1% vs 1.8%), whereas the stenting group had less disabling or fatal stroke
174 beyond 30 days than that in medical group (2.2% vs 6.2%).¹⁹

175 The choice for ICAS treatment between medical therapy and stenting remains
176 incompletely settled, at least for certain high-volume centers and for certain
177 patient groups in a Chinese population. Furthermore, the recurrent stroke risk
178 in the real world remains high despite maximal medical therapy.²⁹ Since the
179 SAMMPRIS trial, an ever-increasing number of PTAS procedures surged
180 beyond guidelines due to increased demand for ICAS treatment in China. The
181 research community has maintained interest in tackling this important cause
182 of stroke. Intracranial stenting with Wingspan is still awaiting a safe
183 landing.^{30,31}

184

185 **3.4 Hypothesis and rationale**

186 It may be hypothesized that the clinical superiority observed in carefully
187 selected patients in high-volume center who received medical therapy had
188 diminished, making stenting a more favorable treatment strategy in
189 comparison. As compared to the design of the SAMMPRIS trial, we thus feel
190 that there is the need for a refined randomized trial reevaluating the role of
191 stenting for ICAS. In the CASSISS trial, patients in both treatment groups
192 have been followed up for 3 more years to establish whether early benefit in
193 the medical group would persist over longer follow-up, or whether the medical
194 group would have a high incidence of late stroke that would eliminate the
195 early efficacy gap between groups.

196

197 **3.5 Objectives**

198 **3.5.1 Primary objective**

199 To determine whether PTAS (using the Gateway PTA balloon catheter and
200 Wingspan Stent System, Stryker, Fremont, CA, USA) combined with medical
201 therapy is superior to medical therapy alone for preventing the primary

202 outcome (stroke or death within 30 days after enrollment, or stroke in the
203 territory of the symptomatic intracranial artery between 30 days through 1
204 year in patients with recent TIA or non-disabling stroke caused by 70% to
205 99% stenosis of a major intracranial artery).

206

207 3.5.2 Secondary objectives

208 To compare outcomes between groups in terms of:

- 209 • Disabling stroke or death beyond 30 days through 3 years;
- 210 • Complication rates associated with stenting procedures;
- 211 • Restenosis (>50%) related to stenting within a follow-up of 3 years;
- 212 • Any stroke, severe TIA, or cardiovascular events within a follow-up of 3
213 years;
- 214 • National Institutes of Health Stroke Scale (NIHSS), mRS, and Barthel
215 index assessment within a follow-up of 3 years;
- 216 • The compliance rate of the patients with regular medical therapy within a
217 follow-up of 3 years;
- 218 • Death rate in both arms within a follow-up of 3 years.

219

220 **4. STUDY DESIGN**

221 This trial is a prospective, multi-center, open-label, randomized control trial
222 that will be conducted in 8 high-volume centers in China Mainland. Patients
223 who meet inclusion criteria are randomized (1:1) to medical therapy alone or
224 to PTAS plus medical therapy. This trial aims to enroll 380 cases. This sample
225 size is large enough to result in acceptable data about safety and efficacy. At
226 each investigational site, the local treating team will consist of at least a
227 neurologist, a neurosurgeon, a neuroradiologist, and a research coordinator.
228 The local treating team conducted enrollment after they reviewed the
229 qualification of each patient. Patients assigned to the medical group will be
230 discharged without further intervention. They will be administered aspirin 100
231 mg plus clopidogrel 75 mg per day for 90 days (aspirin alone per day
232 thereafter). Medical therapy will be identical in both arms and will be similar to
233 the previously-described risk factor management for the SAMMPRIS trial and
234 AHA/ASA guidelines.^{19 32} Patients assigned to the PTAS group will receive
235 PTAS within 3-5 business days after enrollment. All patients will be followed-
236 up in outpatient consultation or by telephone contact with the site
237 investigators at 30-day, 1-year, 2-year, and 3-year marks until the last patient
238 enrolled finishes 3-year follow-up or if patients die before the close-out visit
239 (see flow chart).

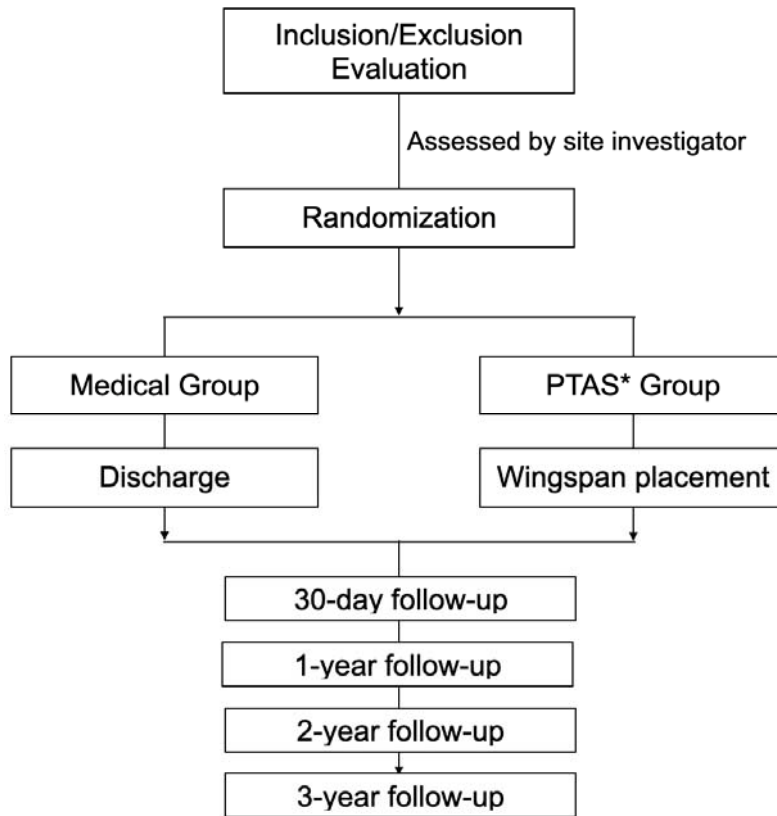
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241 Expected enrollment initiation date: March, 2014

242 Expected enrollment completion date: March, 2017

243 Expected study end date: March, 2020

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Flow Chart

*PTAS, percutaneous transluminal angioplasty and stenting

250 5. STUDY POPULATION

251

252 5.1 Population

253 Patients with recent TIA or stroke caused by 70% to 99% stenosis of a major
 254 intracranial artery. The stenotic degree will be determined on catheter
 255 angiogram using the criteria of the Warfarin-Aspirin Symptomatic Intracranial
 256 Disease Study [WASID]³³).

257

258 5.2 Credentialing of the participating centers and center eligibility

259 Centers are required to have a team consisting of a neurologist, a
 260 neurosurgeon, a neuroradiologist, and a research coordinator. The
 261 randomized trial will not begin until the clinical results of the participating
 262 centers have been certified. All the centers who are interested in this trial will
 263 perform a competitive registration study of recruiting a consecutive 100 PTAS
 264 as a pre-clinical trial within a duration of 8 to 10 months. Certification will be
 265 achieved by participating centers, whose clinical results are audited by means
 266 of a validated selection process. Participating centers meet the following
 267 criteria will be included in the randomized trial: 1) the annual volume of the
 268 cases treated with intracranial stenting for ICAS over the past three years was
 269 more than 30; 2) within the lead-in phase period of eight months, more than
 270 five cases will be performed by a single principal operator; 3) less than 15%
 271 stroke or death rate within 30 days after the revascularization procedure of
 272 the qualifying lesion.

273 There will be 10 high-volume candidate sites (all tertiary hospitals), involved in
 274 a competitive registration study of recruiting a combined total of 100
 275 consecutive patients treated with PTAS:

276

Table: 10 candidate enrollment sites

#	Sites
1	Xuanwu Hospital, Capital Medical University, Beijing, China
2	The 1st Affiliated Hospital of Harbin Medical University, Harbin, China
3	Henan Provincial People's Hospital, Zhengzhou, China
4	Tangdu Hospital of Air Force Medical University, Xi'an, China
5	Beijing Hospital, Beijing, China
6	Qilu Hospital of Shandong University, Ji'nan, China
7	PLA Strategic support Force Characteristic Medical Center, Beijing,

	China
8	The 2nd affiliated Hospital of Guangzhou Medical University, Guangzhou, China
9	Tianjin Huanhu Hospital, Tianjin, China
10	Guangdong Province Hospital of Traditional Chinese Medicine, Guangzhou, China

277

278 **5.3 Inclusion criteria**

- 279 1. Eligible patients aged between 30 and 80 years; intracranial arterial
280 stenosis related to the following non-atherosclerotic factors will be not be
281 considered: arterial dissection, moyo-moya disease; vasculitic disease;
282 herpes zoster, varicella zoster or other viral vasculopathy; neurosyphilis;
283 any other intracranial infection; any intracranial stenosis associated with
284 cerebrospinal fluid pleocytosis; radiation-induced vasculopathy;
285 fibromuscular dysplasia; sickle cell disease; neurofibromatosis; benign
286 angiopathy of central nervous system; postpartum angiopathy; suspected
287 vasospastic process, and suspected recanalized embolus;
- 288 2. Symptomatic intracranial stenosis: presented with transient ischemic
289 stroke (TIA) or stroke within the past 12 months attributed to 70%-99%
290 stenosis of a major intracranial artery (ICA, MCA [M1], vertebral artery, or
291 basilar artery [BA]);
- 292 3. Degree of stenosis: 70%–99%; stenosis degree must be confirmed by
293 catheter angiography for enrollment in the trial;
- 294 4. Remote infarctions on MRI scan, which can be accounted for by the
295 occlusion of the terminal cortical branches or hemodynamic compromise
296 (perforator occlusion excluded). Infarction due to perforators occlusion is
297 defined as basal ganglia or brainstem/thalamus infarction related with M1
298 or BA stenosis;
- 299 5. Expected ability to deliver the stent to the lesion;
- 300 6. All the patients should be performed with stenting beyond a duration of
301 three weeks from the latest ischemic symptom onset;
- 302 7. No recent infarctions identified on MRI (indicated as high signals on DWI
303 series) upon enrollment;
- 304 8. No massive cerebral infarction (>1/2 MCA territory), intracranial
305 hemorrhage, epidural or sub-dural hemorrhage, and intracranial brain
306 tumor on CT or MRI scan;
- 307 9. mRS scale score of ≤ 2 ;

- 308 10. Target vessel reference diameter must be measured to be 2.00 mm to
309 4.50 mm; target area of stenosis is ≤ 14 mm in length;
- 310 11. No childbearing potential or has a negative pregnancy test within the past
311 one week prior to study procedure; female patients had normal menses in
312 the last 18 months;
- 313 12. Patient is willing and able to return for all follow-up visits required by the
314 protocol;
- 315 13. Patients understand the purpose and requirements of the study and have
316 signed informed consent form.

317

318 **5.4 Exclusion criteria**

- 319 1. Refractory to general anesthesia; not able to be overcome by pre-
320 treatment with medical therapy
- 321 2. Any condition that precludes proper angiographic assessment
- 322 3. Tandem extracranial or intracranial stenosis (70%–99%) or occlusion that
323 is proximal or distal to the target intracranial lesion
- 324 4. Bilateral intracranial VA stenosis of 70%–99% and uncertainty about
325 which lesion is symptomatic (for example, if patient has pon, midbrain,
326 temporal and occipital symptoms)
- 327 5. Presence of a previously placed intravascular stent or graft in the
328 ipsilateral distribution within 30 days
- 329 6. Previous treatment of target lesion with a stent, angioplasty, or other
330 mechanical device, or plan to perform staged angioplasty followed by
331 stenting of target lesion
- 332 7. Severe vascular tortuosity or anatomy that would preclude the safe
333 introduction of a guiding catheter, guiding sheath or stent placement
- 334 8. Plan to perform concomitant angioplasty or stenting of an extracranial
335 vessel tandem to an ipsilateral intracranial stenosis
- 336 9. Presence of intraluminal thrombus proximal to or at the target lesion
- 337 10. Any aneurysm proximal to or distal to intracranial stenotic artery
- 338 11. Intracranial tumors or any intracranial vascular malformations
- 339 12. Computed tomographic or angiographic evidence of severe calcification
340 at target lesion
- 341 13. Thrombolytic therapy within 24 hours before enrollment
- 342 14. Evolving stroke or progressive neurologic signs within 24 hours before
343 enrollment

- 344 15. Stroke of sufficient size (>5 cm on CT or MRI) to place patient at risk of
345 hemorrhagic transformation during the procedure; hemorrhagic
346 transformation of an ischemic stroke within the past 15 days
- 347 16. Previous spontaneous intracerebral (parenchymal) or other intracranial
348 (subarachnoid, subdural, or epidural) hemorrhage within 30 days
- 349 17. Untreated chronic subdural hematoma >5 mm in thickness
- 350 18. Other cardiac sources of emboli such as left ventricular aneurysms,
351 intracardiac filling defect, cardiomyopathy, aortic or mitral prosthetic heart
352 valve, calcified aortic stenosis, endocarditis, mitral stenosis, atrial septal
353 defect, atrial septal aneurysm, left atrial myxoma
- 354 19. Myocardial infarction within previous 30 days
- 355 20. Chronic atrial fibrillation; any episode of paroxysmal atrial fibrillation within
356 the past six months, or history of paroxysmal atrial fibrillation requiring
357 chronic anticoagulation
- 358 21. Intolerance or allergic reaction to any of the medical therapy, including
359 aspirin, clopidogrel, heparin, and local or general anesthetics
- 360 22. History of life-threatening allergy to contrast medium. If not life threatening
361 and can be effectively pre-treated, patient can be enrolled at physicians'
362 discretion
- 363 23. Recent gastrointestinal bleed that would interfere with antiplatelet therapy
- 364 24. Active bleeding diathesis or coagulopathy; active peptic ulcer disease,
365 major systemic hemorrhage within 30 days, active bleeding diathesis,
366 platelets count <125,000, hematocrit <30, Hgb <10 g/dl, uncorrected
367 INR >1.5, bleeding time >1 minute beyond upper limit normal, or heparin-
368 associated thrombocytopenia that increases the risk of bleeding,
369 uncontrolled severe hypertension (systolic BP>180mm hg or diastolic
370 BP>115mm hg), severe liver impairment (AST or 25. ALT >3 times normal,
371 cirrhosis), creatinine >265.2 mmol/l (unless on dialysis). Major surgery
372 (including open femoral, aortic, or carotid surgery) within previous 30 days
373 or planned in the next 90 days after enrollment
- 374 25. Indication for warfarin or heparin beyond enrollment (exceptions allowed
375 for use of systemic heparin during stenting procedure or subcutaneous
376 heparin for deep venous thrombosis prophylaxis while hospitalized)
- 377 26. Inability to understand and cooperate with study procedures or sign
378 informed consent
- 379 27. Severe dementia or psychiatric problems that prevent the patients from
380 following an outpatient program reliably
- 381 28. Pregnancy or of childbearing potential and unwilling to use contraception
382 for the duration of this study

- 383 29. Actively participating in another drug or device trial that has not completed
384 the required protocol follow-up period
385

386 **6. Methods**

387

388 **6.1 Primary outcomes**

- 389 • Stroke or death within 30 days after enrollment;
- 390 • Stroke in the territory of the symptomatic intracranial artery (SIT) between
- 391 30 days and 1 year

392

393 **6.2 Secondary outcomes**

- 394 • Disabling stroke or death beyond 30 days through 3 years in both arms;
- 395 • Complication rates associated with stenting procedures;
- 396 • Restenosis (>50%) related to stenting within a follow-up of 3 years;
- 397 • Any stroke, severe TIA, or cardiovascular events within a follow-up of 3
- 398 years;
- 399 • National Institutes of Health Stroke Scale (NIHSS), mRS, and Barthel
- 400 index (BI) assessment within a follow-up of 3 years;
- 401 • The compliance rate of the patients with regular medical therapy within a
- 402 follow-up of 3 years;
- 403 • Death rate in both arms within a follow-up of 3 years.

404

405 **6.3 Definitions of outcomes**

- 406 1. Stroke is defined as the rapid loss of brain functions due to disturbance in
- 407 the blood supply to the brain that persists beyond 24 hours. Stroke is
- 408 diagnosed by an independent outcome committee which is composed
- 409 with experienced neurologists. They will collect additional key neuro-
- 410 images (CT or MR scans) as adjunct evidence for outcome classification
- 411 of ischemic or hemorrhagic stroke;
- 412 2. Ischemic stroke is defined as a new focal neurological deficit of sudden
- 413 onset lasting at least 24 hours that is not associated with a hemorrhage
- 414 on brain CT or MRI. Ischemic strokes are further classified by the
- 415 neurologic adjudicators as being either in or out of the territory of the
- 416 qualifying artery;
- 417 3. Hemorrhagic stroke is defined as parenchymal, sub-arachnoid, or intra-
- 418 ventricular hemorrhage detected by CT or MRI that is associated with new
- 419 neurological signs or symptoms lasting >24 hours or a seizure;
- 420 4. Death, any of the following criteria:

- 421 a) Procedure-related deaths, including those related to a complication
422 of the procedure or treatment for a complication of the procedure.
- 423 b) Death to due to cardiac cause, e.g., myocardial infarction, cardiac
424 tamponade, and worsening heart failure
- 425 c) Death of other cause (e.g., malignancy, trauma and suicide)
- 426 d) Sudden or unwitnessed death
- 427 e) Death of unknown cause
- 428 5. Disabling stroke is defined by any of the following:
- 429 a) a modified Rankin score of 3 or more, on a scale of 0 to 6, with
430 higher scores indicating greater disability;
- 431 b) an increase in at least one mRS category from an individual's pre-
432 stroke baseline
- 433 c) a score on the composite National Institutes of Health Stroke Scale
434 (NIHSS) of 7 or more, on a scale of 0 to 42, with higher scores
435 indicating more severe deficits;
- 436 d) an increase in at least 4 NIHSS scales from pre-stroke baseline.
- 437 6. Complication rates associated with stenting procedures: refer perforator
438 occlusion, guidewire perforation, artery-to-artery embolism, stent
439 thrombosis, or reperfusion hemorrhage within 72 hours after PTAS
440 procedures.
- 441 7. Restenosis rate: if patients have follow-up vascular imaging, the imaging
442 modality will be recorded, in addition to the percent stenosis of the target
443 lesion. Re-stenosis is defined as 50% narrowing or greater irrespective of
444 symptoms.
- 445 8. TIA: duration of a focal or global neurological deficit <24 h, any variable
446 neuroimaging does not demonstrate a new hemorrhage or infarction;
- 447 9. Severe TIA refers to rapidly developed clinical signs of focal or global
448 disturbance of cerebral function lasting longer than 10 minutes but fewer
449 than 24 hours, without apparent nonvascular cause.
- 450 10. Cardiovascular events: refer a class of events that is related to stenting or
451 medical therapy, which includes coronary artery diseases (CAD) such as
452 angina and myocardial infarction.
- 453 11. BI, mRS and NIHSS: please refer the appendix 12.1, 12.2 and 12.3.
- 454 12. Compliance of drug: patients will be contacted at 30-day, 1-year, 2-year
455 and 3-year after enrollment, to gather information regarding the use of
456 anti-platelet drugs, changes in prescribed drugs, medical condition and
457 quality of life.

458 a) very good, 80% - 120%;

459 b) good, 60% - 79%;

460 c) fair, 40% - 59%;

461 d) poor, < 40%.

462

463

464 **6.4 Definitions of other parameters**

465 6.4.1 Major vascular complications

466 1. Non-neurovascular death: e.g., trauma, suicide, malignancy, or
467 cardiovascular mortality;

468 2. Major vascular complication: e.g., aortic dissection, aortic rupture, or
469 annulus rupture;

470 3. Access site of access-related vascular injury (dissection, stenosis,
471 perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma,
472 irreversible nerve injury, or percutaneous closure device failure) leading to
473 death, life-threatening or major bleeding, or neurological impairment;

474 4. Distal cerebral embolism from a vascular source requiring surgery or
475 endovascular intervention or irreversible neurological damage;

476 5. Any new ipsilateral lower extremity ischemia documented by patient
477 symptoms, physical examination, and/or decreased or absent blood flow
478 on lower extremity angiogram;

479 6. surgery for access site-related nerve injury;

480 7. permanent access site-related nerve injury.

481

482 6.4.2 Minor vascular complications

483 1. Access site of access-related vascular injury (dissection, stenosis,
484 perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma,
485 or percutaneous closure device failure) not leading to death, life-
486 threatening or major bleeding, or neurological impairment;

487 2. Distal cerebral embolism treated with mechanical thrombectomy not
488 resulting in irreversible neurological damage;

489 3. Any unplanned endovascular stenting or surgical intervention not meeting
490 the criteria for a major vascular complication;

491 4. Vascular repair: e.g., ultrasound-guided compression or injection
492 embolization, transcatheter embolization or stent-graft;

493 5. Percutaneous closure device failure.

494 **6.5 Treatment assignment**

495 Eligible patients will be enrolled with their baseline data entered into a web-
496 based database system. Patients will be randomized (1:1) to medical therapy
497 alone or medical therapy plus stenting using Wingspan. There will be no
498 blinding. When a patient is included for participation, site investigator will be
499 informed. The patients will be excluded from the ITT analysis if they sign the
500 ICF while they don't meet the criteria of inclusion and exclusion after central
501 image Corelab adjudication.

502 A summary will be made of patients who are randomized to PTAS group but
503 do not undergo surgery, and the patients who are randomized to medical
504 therapy but receive surgery. Compliance will be assessed by the investigator
505 at each visit using information provided by the care-giver or patients
506 themselves. This information should be recorded in the source document at
507 each visit.

508

509 **6.6 Randomization and numbering**

510 A central randomization system, IVRS (Interactive Voice Response System,
511 Clinicalsoft Company Limited, Beijing, China; <http://ivr.clinicalsoft.cn>) will be
512 used for patient randomization. Each patient has its unique ID number (center
513 number plus screening order number) in this trial. This center number will be
514 assigned to each participating center. Once the patients or their legal
515 representatives sign the informed consent form (ICF) at each center, they will
516 be assigned with a screening order number. At each center, the screening
517 order number will be in order of the patients' enrollment (e.g., 001, 002, 003
518 and so on).

519

520 **6.7 Medical group**

521

522 Patients randomized to medical group will received medical therapy and be
523 discharged without further intervention.

524

525 **6.7.1 Medical therapy**

526 Medical therapy will be identical in both arms and will be similar to the
527 previously described risk factor management for the SAMMPRIS trial. In brief,
528 it includes both aspirin 100 mg plus clopidogrel 75 mg per day for 90 days
529 (aspirin 100 mg alone per day thereafter) and management of risk factors.

530 The drugs used in the trial are commercially available in China. Several
531 generic aspirin or clopidogrel are available and allowed to be used. Medical
532 therapy regimen, including DAPT and statin will be purchased by the patients

533 or their family member, who later received various degrees of reimbursement
534 from the Chinese social security system.

535

536 6.7.2 Management of risk factors

537 Risk factor control is based on the 2011 AHA/ASA guidelines³² and the
538 SAMMPRIS¹⁹ trial protocol. Medical management of risk factors consists of
539 normalizing low-density lipoprotein (LDL-C) (statins, target LDL-C <2.58
540 mmol/l [100 mg/dl]), hypertension (systolic pressure <140 mmHg and a
541 diastolic pressure <90 mmHg), glucose disorder (in diabetic patients,
542 hemoglobin A1c [HbA1c] will be checked at enrollment and during each
543 clinical visit with a target level of <6.5%), and lifestyle modification. Intensive
544 management of risk factors is applicable to all the included patients (e.g.,
545 hypertension, lipid disorder, diabetes mellitus, overweight, obesity, physical
546 inactivity, and cigarette smoking).

547

548 6.7.3 Health education and lifestyle modification

- 549 1. Health education and lifestyle modification: quit smoking, moderate-
550 intensity physical exercises (at least 3 times per week for 30 min per
551 session).
- 552 2. Obesity: BMI should be maintained below 25 kg/m². Weight reduction is
553 associated with a lowering in BP and may thereby reduce stroke risk.

554

555

556 **6.8 PTAS group**

557

558 Patients randomized to PTAS group are to be scheduled for surgery within
559 three to five business days after enrollment. The study protocol requires that
560 the stenting procedure be performed by a qualified operator at each site.

561 6.8.1 PTAS procedure

562 Patients randomized to stenting will be placed on DAPT (aspirin, 100 mg daily
563 and clopidogrel 75 mg daily) for 3-5 consecutive days before the procedure.
564 No loading dose will be allowed. The study protocol requires that the PTAS
565 procedure is typically performed under general anesthesia by a credentialed
566 interventionalist who should be the primary operator. The procedure is typically
567 performed via a transfemorally placed 6F-long sheath or guiding catheter. The
568 stenotic lesion is primarily crossed with a standard 0.014" microcatheter
569 microwire system under high magnification fluoroscopic roadmap control.
570 Once across the lesion, the microcatheter is exchanged over a 300-cm,

571 0.014" microwire for a Gateway balloon catheter. After angioplasty, the
572 balloon catheter is exchanged for a Wingspan stent delivery system and the
573 self-expanding Wingspan stent is deployed across the stenosis. If the residual
574 stenosis after inserting the Wingspan stent is >50%, the study protocol allows
575 for postdilation with a new balloon catheter. The protocol required frequent
576 measurements of blood pressure during the procedure and at least 1
577 measurement every half an hour during the next 24 hours while the patient is
578 monitored. The patient will be continued on aspirin, 100 mg daily, and
579 clopidogrel, 75 mg daily, for the next 90 days and subsequently on aspirin
580 alone. Risk factor control should be applied thereafter.

581

582 6.8.2 Rescue therapy for PTAS

- 583 1. If the residual stenosis is >50% after the primary Wingspan placement,
584 study protocol allows for the postdilation with a new balloon catheter to
585 achieve better angioplasty outcome.
- 586 2. If the initial Wingspan stent could not be delivered to the target lesion, the
587 interventionalist can try to deliver a second Wingspan stent.
- 588 3. If the second Wingspan stent cannot be delivered to the target lesion, the
589 interventionalist has the following options: a) angioplasty alone with
590 Gateway balloon catheter; b) using non-Wingspan stent; c) procedure
591 aborted.
- 592 4. If an ischemic stroke occurs or an intraluminal thrombus develops during
593 the procedure, the interventionalist or stroke neurologist (if available)
594 should administrate appropriate treatment. This may include intravenous
595 or intraarterial use of thrombolytic therapy, e.g., glycoprotein IIb-IIIa
596 Inhibitor (Tirofiban).
- 597 5. If a major dissection, other occlusive complication, or stent misplacement
598 occurs that requires placement of a second Wingspan stent, this may be
599 done as a rescue procedure. In the meantime, neuro ICU will provide
600 reservations to deal with patients with serious complications.

601

602 6.9 Follow-up schedule

603 Clinical assessment of patients will be conducted in outpatient consultation or
604 by telephone contact with the site investigators at 30-day, 1-year, 2-year, and
605 3-year or if the patients died before the close-out visit. At each follow-up visit,
606 patients will be examined by study physicians who also manage the patients'
607 vascular risk factors. Imaging assessment will be achieved by head MRI, CTA,
608 MRA, or DSA at each visit if possible.

609

610

Table: follow-up schedule

	In-hospital			Follow-up (Paper-based CRF)			
	Baseline	Procedure	Discharge	30- day	1- year	2- year	3- year
ICF	<input checked="" type="checkbox"/>						
In-/Exclusion criteria	<input checked="" type="checkbox"/>						
Demographics	<input checked="" type="checkbox"/>						
Medical history	<input checked="" type="checkbox"/>						
Physical exam	<input checked="" type="checkbox"/>			<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Neurological status							
NIHSS	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
mRS	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Barthel Index	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Lab test	<input checked="" type="checkbox"/>				<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Neuro-imaging							
CT/MRI (DWI)	<input checked="" type="checkbox"/>				<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
TCD/CTA/MRA	<input checked="" type="checkbox"/>				<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
CTP/PWI	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>			<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
DSA	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>			<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Medication	<input checked="" type="checkbox"/>			<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
AE/SAE		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

611

612

613 6.9.1 Baseline

614 At baseline, the following parameters should be documented:

615 I. Date of ICF

616 II. Demographics

617 III. Medical history

618 a. Present history

619 b. Previous history, e.g., hypertension, diabetes, lipid disorder,
620 coronary and peripheral artery disease, smoking and alcohol
621 abuse, etc.

622 IV. Clinical status

623 a. Physical examination

624 b. Vital signs: blood pressure, pulse rate, respiratory rate and body
625 temperature

626 c. ECG

627 d. BMI

628 V. Neurological status

629 a. NIHSS

630 b. mRS

- 631 c. Barthel Index
- 632 VI. Lab test
- 633 a. Routine blood test
- 634 b. Liver function: e.g., ALT, AST, etc.
- 635 c. Renal function: e.g., Cr, BUN, etc.
- 636 d. Renal damage: proteinuria (according to site's preference and
- 637 facilities)
- 638 e. FBG and HbA1c
- 639 f. Lipid level: LDL, HDL and TC
- 640 g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.
- 641 h. Inflammation markers: CRP
- 642 i. Pregnancy test
- 643 VII. Neuro-imaging
- 644 a. Cranial CT/MR (DWI)
- 645 b. TCD/CTA/MRA
- 646 c. CTP/PWI parameters: CBF, CBV, MTT and TTP
- 647 d. DSA
- 648
- 649 6.9.2 Procedure (for PTAS group)
- 650 During the procedure, the following parameters should be documented:
- 651 I. Date of the procedure
- 652 a. delayed procedure: beyond 5 business day after enrollment
- 653 b. procedure on time: within 5 business day after enrollment
- 654 II. Operator of the procedure
- 655 III. Anesthesia: general or local
- 656 IV. Morphological characteristics of the lesion on DSA
- 657 a. side: right or left
- 658 b. size: diameter and length (mm)
- 659 c. location: M1, BA, ICA or VA
- 660 d. stenotic degree (%) determined using the WASID criterion³³
- 661 e. Mori classification: type A, B or C³⁴ (Appendix 12.4)
- 662 f. TICl perfusion categories³⁵ (Appendix 12.5)

663 g. ASITN/SIR collateral flow grading system³⁵ (Appendix 12.6)

664 V. Type of procedures

665 a. angioplasty plus stent placement

666 b. angioplasty alone

667 c. none

668 VI. Angioplasty balloon

669 a. size: diameter and length (mm)

670 b. type: Gateway or others

671 c. number: 1 or more

672 VII. Stent delivered

673 a. size: diameter and length (mm)

674 b. type: Wingspan or others

675 c. number: 1 or more

676 VIII. Residual stenosis (%)

677 IX. Use of post-dilation:

678 a. yes or no

679 b. if yes, type and size of the balloon used

680 c. inflation pressure (atm)

681 d. residual stenosis after post-dilation

682 X. Rescue therapy

683 XI. Post-PTAS neurological status

684 a. NIHSS

685 b. mRS

686 c. Barthel Index

687 XII. AE/SAE

688

689 6.9.3 Discharge

690 Before discharge, the following parameters should be documented:

691 I. Neurological status

692 a. NIHSS

693 b. mRS

694 c. Barthel Index

695 II. AE/SAE

696

697 6.9.4 30-day follow-up

698 At 30-day follow-up, the following parameters should be documented:

699 I. Clinical status

700 a. Physical examination

701 b. Vital signs: blood pressure, pulse rate, respiratory rate and body
702 temperature

703 c. ECG

704 d. BMI

705 II. Neurological status

706 a. NIHSS

707 b. mRS

708 c. Barthel Index

709 III. Medication

710 IV. AE/SAE

711

712 6.9.5 1-year follow-up

713 At 1-year follow-up, the following parameters should be documented:

714 I. Clinical status

715 a. Physical examination

716 b. Vital signs: blood pressure, pulse rate, respiratory rate and body
717 temperature

718 c. ECG

719 d. BMI

720 II. Neurological status

721 a. NIHSS

722 b. mRS

723 c. Barthel Index

724 III. Lab test

725 a. Routine blood test

726 b. Liver function: e.g., ALT, AST, etc.

- 727 c. Renal function: e.g., Cr, BUN, etc.
- 728 d. Renal damage: proteinuria (according to site's preference and
729 facilities)
- 730 e. FBG and HbA1c
- 731 f. Lipid level: LDL, HDL and TC
- 732 g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.
- 733 h. Inflammation markers: CRP
- 734 IV. Neuro-imaging
- 735 a. Cranial CT/MR (DWI)
- 736 b. TCD/CTA/MRA
- 737 c. CTP/PWI parameters: CBF, CBV, MTT and TTP
- 738 d. DSA
- 739 V. Medication
- 740 VI. AE/SAE
- 741
- 742 6.9.6 2-year follow-up
- 743 At 2-year follow-up, the following parameters should be documented:
- 744 I. Clinical status
- 745 a. Physical examination
- 746 b. Vital signs: blood pressure, pulse rate, respiratory rate and body
747 temperature
- 748 c. ECG
- 749 d. BMI
- 750 II. Neurological status
- 751 a. NIHSS
- 752 b. mRS
- 753 c. Barthel Index
- 754 III. Lab test
- 755 a. Routine blood test
- 756 b. Liver function: e.g., ALT, AST, etc.
- 757 c. Renal function: e.g., Cr, BUN, etc.
- 758 d. Renal damage: proteinuria (according to site's preference and
759 facilities)

- 760 e. FBG and HbA1c
- 761 f. Lipid level: LDL, HDL and TC
- 762 g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.
- 763 h. Inflammation markers: CRP

764 IV. Neuro-imaging

- 765 a. Cranial CT/MR (DWI)
- 766 b. TCD/CTA/MRA
- 767 c. CTP/PWI parameters: CBF, CBV, MTT and TTP
- 768 d. DSA

769 V. Medication

770 VI. AE/SAE

771

772 6.9.7 3-year follow-up

773 The following parameters should be documented:

774 I. Clinical status

- 775 a. Physical examination
- 776 b. Vital signs: blood pressure, pulse rate, respiratory rate and body
777 temperature
- 778 c. ECG
- 779 d. BMI

780 II. Neurological status

- 781 a. NIHSS
- 782 b. mRS
- 783 c. Barthel Index

784 III. Lab test

- 785 a. Routine blood test
- 786 b. Liver function: e.g., ALT, AST, etc.
- 787 c. Renal function: e.g., Cr, BUN, etc.
- 788 d. Renal damage: proteinuria (according to site's preference and
789 facilities)
- 790 e. FBG and HbA1c
- 791 f. Lipid level: LDL, HDL and TC

792 g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.

793 h. Inflammation markers: CRP

794 IV. Neuro-imaging

795 a. Cranial CT/MR (DWI)

796 b. TCD/CTA/MRA

797 c. CTP/PWI parameters: CBF, CBV, MTT and TTP

798 d. DSA

799 V. Medication

800 VI. AE/SAE

801

802 **6.10 Consent withdrawal**

803 Patients may voluntarily withdraw consent to participate in the study for any
804 reason at any time. Consent withdrawal occurs only when a patient: 1) does
805 not want to participate in the study anymore; 2) or does not want any further
806 visits or assessments; 3) or does not want any further study-related contacts.

807 When a patient withdraws consent, the investigator is required to determine
808 the primary reason for this decision and record this information. Further
809 attempts to contact the patient are not allowed unless safety efficacy require
810 follow-up. After withdrawal, patients will not be replaced by others and their
811 randomized ID number will not be re-used.

812

813 **6.11 Follow-up of subjects withdrawn from treatment assignment**

814 Some cases may withdraw from treatment assignment. Since the statistical
815 analysis is planned for ITT principle, they will be analyzed in the group that
816 they were originally allocated to.

817

818 **6.12 Lost for follow-up**

819 For patients whose status are unclear because they fail to appear for study
820 visits without stating an intention to withdraw, the investigator should show
821 "due diligence" by contacting the patient, family or family physician as agreed
822 in ICF and by documenting in the source documents steps taken to contact
823 the patient, e.g., dates of telephone calls, registered letters, etc. Lost for
824 follow-up could be accounted by no reply although try to contact the cases
825 three times or more. A patient should not be formally considered lost to follow-
826 up until his/her scheduled end of study visit would have occurred.

827

828 6.13 Study completion and post-study treatment

829 At the end of the study visit, the investigator should provide follow-up medical
830 care for all patients who are prematurely withdrawn from the study or refer
831 them for appropriate ongoing care. When the patient has completed all
832 scheduled study assessments, the investigator is required to inform to record
833 the patient completion in the EDC system.

834

835 6.14 Premature termination of the study

836 During the trial, AEs or SAEs will be reported to DSMB. The DSMB will
837 monitor SAEs, major safety events, device and procedure failures and any
838 device-related adverse events. In the current trial, SAEs mainly refer disabling
839 stroke, symptomatic intracranial hemorrhage or death within 1 year after
840 enrollment and all-cause death within a follow-up 3 years. The stopping rules
841 will be developed by DSMB and the advices of DSMB will be sent to the
842 executive and steering committee of the study. The Executive and Steering
843 Committee will be responsible for informing the EC whether the advices are
844 fully implemented or not.

845

846 6.15 Outcome assessment

847 This is a multicenter phase IV RCT with open-label treatment and blinded
848 outcome assessment. Outcome assessment will be sent to an independent
849 Outcome Committee. The committee is composed of experienced
850 neurologists who are not involved in the study, will be blinded to the treatment
851 assignment. All the outcome will be adjudicated by the outcome committee,
852 and a consensus will be reached by a third clinician in case of discrepancies.

853

854

855

856

857 **7. SAFETY MONITORING**

858 **7.1 Adverse events (AE)**

859 AE is defined as any unfavorable and unintended sign, symptom or disease
860 that occurs to a subject while enrolled in a clinical investigation, whether or
861 not considered related to the study intervention or device. Medical conditions
862 that exist at study enrollment are not considered an AE unless condition
863 worsens after use of the study intervention or device.

864

865 **7.2 Serious adverse events (SAE)**

866 7.2.1 Definition of SAE

867 A SAE is any medical experience regardless of its relationship to the
868 investigational device or study devices that occurs during subject enrollment
869 in this trial that results in any of the following:

870 ☞ need to be hospitalized or prolonged hospitalization;

871 ☞ persistent or significant disability/incapacity;

872 ☞ death of the study subject;

873 ☞ necessitates an intervention to prevent a permanent impairment of a body
874 function or permanent damage to a body structure

875 ☞ or causing congenital anomalies/birth defects.

876

877 7.2.2 SAE reporting

878 All SAEs will be recorded in the table of CRF. The details of the SAEs,
879 including starting time, ending time, duration, treatment, outcome, and the
880 relationship with intervention will be recorded as well. Frequency of SAEs will
881 be summarized according to the assignments. All recorded AEs/SAEs will be
882 reported to the investigator. SAEs that result in death or life-threatening stroke
883 will be reported to DSMB/EC within 14 days after the investigator is informed
884 for the first time. In the current trial, SAEs mainly refer disabling stroke,
885 symptomatic intracranial hemorrhage or death within 1 year after enrollment
886 and all-cause death within a follow-up 3 years. For safety analysis, an
887 independent summary will list SAEs related to intervention in PTAS group.

888

889 7.2.3 Management and follow-up of AEs/SAEs

890 Investigators should take appropriate treatment for AEs to ensure the safety
891 of patients and track all AEs/SAEs until they are properly resolved, or the
892 condition is stable. Additional medical procedures and/or referral to a medical

893 specialist may be required to confirm whether the patients are qualified to
894 continue to participate in the study.

895

896 **8. DATA MANAGEMENT**

897 **8.1 Study Data Collection**

898 Site coordinator records data by filling out the paper-based CRF for each
899 case. The sponsor (Beijing Xuanwu Hospital) provides CRFs to each site. Site
900 investigator is responsible for that all CRFs are completed, reviewed, and
901 approved. Also, site investigator will sign on CRFs and confirm that clinical,
902 imaging and laboratory data entered into the CRFs are true.

903 Patient ID in CRFs should be recorded in an anonymous form, which are only
904 identified by the patient ID number and Chinese phonetic alphabets (pinyin)
905 initials. CRFs should be filled in with a black ballpen based on the original
906 document. Fill in “not done” for missing data; fill in “not applicable” if not
907 applicable; fill in “unknown” for unknown data.

908 If the data entered into CRFs needs to be revised, cross out the error with a
909 single line so that it can still be seen clearly, and then fill in the correct data
910 next to it. The revisions should be approved and signed by the site
911 investigator. If necessary, the reason for the revisions should be indicated.
912 Site investigator will review the integrity and accuracy of the CRFs and make
913 further corrections and amendments if necessary. When the trial is finished,
914 site investigator will send the CRFs to Tigermed Data Management Co., Ltd;
915 (<https://tigermedgrp.com>) for data entry.

916 The data in the paper-based CRFs will be entered into the database by
917 Tigermed Data Management Co., Ltd, with its completeness and accuracy
918 reviewed. The missing data and questioned data are reported in the data
919 query form, which will be sent back to the site investigator for further
920 verification. Site investigator will send back in the resolved query form with
921 signature and date of signing. Tigermed Data Management shall be
922 responsible for entering the resolved results into the database. After the final
923 confirmation is completed and all queries are resolved, the database is
924 updated and locked. Data is transferred from the database directly to the data
925 file (SAS data set) for statistical analysis. The data can be changed after
926 database is unlocked upon reasonable request.

927

928 **8.2 Data Processing and Quality Control**

929 The data entry is performed by the staff trained by Tigermed Data
930 Management Co., Ltd. All the input data should go through verification and
931 range check. The staff will be notified of a possible error, depending on the
932 data validation. The staff will not move on unless the error is resolved.

933 All CRFs will be subject to preliminary inspection for data missing,
934 inconsistency and deviation. Data inconsistency will be completed by
935 electronic tracking and resolved by site coordinators and investigators.

936

937 Each data input will receive regular cross-check within forms. Site
938 coordinators will be informed in case of errors identified. Corrections to the
939 data in CRFs will be made by the site coordinators, and approved by the site
940 investigators.

941

942 The data editing will continue when all data is cleaned. The site coordinators
943 will supervise the verification of on-site source documents. If further data
944 related to the source file is found during the site visit, additional queries will be
945 generated and processed by the site coordinators.

946

947 **8.3 Data storage**

948 The investigator will document adequate records during the conduct of the
949 study. Trial data including patient files, CRFs, ICFs, original copies of results,
950 and imaging outcome, will be kept on files by the investigator for a period of
951 10 years or more.

952

953

954 **9. STATISTICAL ANALYSIS**

955 **9.1 Analysis data set**

956 Full Analysis Set (FAS): all the subjects who are randomized into groups will
957 be included, and the subjects who do not meet the eligible criteria and who
958 withdraw immediately after randomization without receiving any interventions
959 will be excluded. According to the intention-to-treat (ITT) principle, all
960 randomized patients will be analyzed according to the treatment group
961 assigned to them at the time of randomization. All presenting analyses will be
962 conducted in the FAS population unless otherwise specified

963 Per-protocol Set (PPS): PPS refers population who are treated according to
964 the study protocol, e.g., fulfilling eligibility criteria, assigned treatment after
965 randomization, medication and follow-up protocol, and completion of the case
966 report form). PPS analysis was conducted on the population who had not
967 crossovers between groups or significant protocol violations. Crossover
968 population from one arm to the other will not impact the ITT analysis. For
969 PTAS group, significant protocol violations include: 1) use of non-Wingspan
970 stents; 2) delayed procedure of PTAS (beyond 5 business days after
971 enrollment; 3) procedure is aborted before lesion is accessed; 4) procedure is
972 aborted due to total occlusion; 5) receive angioplasty only and others. For
973 other details, please refer to the Statistical Analysis Protocol (SAP) in the
974 Appendix.

975 For other details, please refer to the Statistical Analysis Protocol (SAP) in the
976 Appendix.

977

978 **9.2 Analysis close date**

979 The analysis close date for each arm is at the completion of 3-year follow-up
980 of the last enrolled patient. The primary outcome is based on the exact 3-year
981 time point for each patient, and event.

982

983 **9.3 Sample size calculation**

984 For symptomatic severe (70-99%) intracranial atherosclerotic stenosis, 1 year
985 of ipsilateral stroke risk in medical therapy group WASID study was 18%,³⁶
986 which was 7.3% in a study by the Wingspan stent therapy.²³ At a significance
987 level of 5% on both sides, the absolute difference of 10.7% (relative risk
988 reduction 59%), and a power of 80%, within 12 months of follow-up, a total of
989 302 patients need to be evaluated. Assuming a 20% incidence of loss of
990 follow-up and/or withdrawal, a total of 380 patients, 190 in the stent group and
991 190 in the medical group, are required to be enrolled in this study.

992

993 **10. STUDY COMMITTEES**

994 **10.1 Executive and Steering Committee**

995 Executive committee is composed of principle and site investigators from the
996 participating centers, which is responsible for making decisions about the
997 direction and strategy of the trial. During the trial period, this committee fulfills
998 the coordination, implementation, organize regular meeting, and report
999 progress. Also, it is required to review main trial publications, analysis plan
1000 and publication policy, and consider recommendations of DSMB.

1001

1002 **10.2 Ethics Committee**

1003 The trial should first obtain the written approval from the Ethics committee of
1004 Xuanwu Hospital, Capital Medical University, Beijing, China. The trial will not
1005 enroll patient until the study protocol is approved by the local ethics
1006 committee (EC) in the other sites. In case of any major amendments to the
1007 trial protocol, renewed written approval should be obtained from the ethics
1008 committee. Updated ICF after amendments will be sent to patients in the
1009 active period of the trial. Minor amendments will not be sent to EC.

1010

1011 **10.3 Data and safety Monitoring Board (DSMB)**

1012 An independent DSMB that is composed of neurologist, neurosurgeon,
1013 neuroradiologist and biostatistics experts who are not involved in the conduct
1014 of the trial. DSMB members should not have any scientific or financial
1015 conflicts of interest with the sponsor or investigator. DSMB is responsible for
1016 study conduct, progress and efficacy. By reviewing safety data, DSMB will
1017 advise executive committee to continue, modify or terminate the trial early.

1018

1019 **10.4 Clinical outcome committee**

1020 Clinical outcome assessment will be sent to an independent Outcome
1021 Committee. The committee composed of experienced neurologists who are
1022 not involved in the study, will be blinded to the treatment assignment. All the
1023 outcome will be adjudicated by the outcome committee, and a consensus will
1024 be reached by a third clinician in case of discrepancies. For details, please
1025 refer to *2.9 Assessments of clinical outcome* in the *2. Supplementary Methods*.

1026

1027 **10.5 Imaging outcome committee:**

1028 An independent imaging core-lab, IsCore Image CoreLab (ICIC,
1029 <http://imagecorelabcn.com/>), will be established with the aim of facilitating the
1030 central reading by clinicians and integrating medical imaging at the baseline

1031 control and each clinical visit. For details, please refer to *2.10 Assessments of*
1032 *imaging outcome* in the *2. Supplementary Methods*.

1033

1034

1035 **11. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS**

1036 **11.1 Regulatory and ethical compliance**

1037 The design, implementation and reporting of this trial will follow the principles
1038 of the Declaration of Helsinki (World Medical Association: Declaration of
1039 Helsinki, Ethical Principles for Medical Research Involving Human Subjects -
1040 Version 2008).

1041

1042 **11.2 Recruitment and informed consent form**

1043 Eligible patients who voluntarily agree to participate in the trial will be required
1044 to sign a written informed consent form (ICF). The ICF will be signed by the
1045 patients or his/her legal representative prior to randomization. They will
1046 be informed shortly by the investigators when the treatment is assigned after
1047 central randomization.

1048

1049 **11.3 Responsibilities of the investigator**

1050 Site investigators will review the eligibility of each candidate patient. If the
1051 patient is qualified and interested in this trial, he/she will be given written ICF
1052 to participate. Site investigators are responsible for explaining the research
1053 background, intervention, protocol, benefits, and risks of participating in the
1054 trial. A signed ICF copy will be kept by the patient as part of the study files.
1055 The patient is fully entitled to quit at any circumstance.

1056

1057 **11.4 Public disclosure and publication policy**

1058 As the sponsor of the study, Xuanwu Hospital aims to publicize the primary
1059 and secondary outcome results in a high-impact scientific journal. Database
1060 of this trial will be locked within 3 months when the last enrolled patient
1061 finished the scheduled 3-year follow-up and all the data of the enrolled
1062 patients is completed. A manuscript will be submitted for potential publication
1063 in a scientific journal within 3 months after database lock. The manuscript will
1064 be shared with the financial sponsor(s) 3 months before submission, but the
1065 financial sponsor(s) have no influence on its contents. Anonymous data can
1066 be provided by principal investigators upon reasonable request.

1067

1068

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- 1187

1188 **13. APPENDIX**

1189

1190 **13.1 Barthel Index (BI)**

1191 The Barthel scale is an ordinal scale used to measure performance in
 1192 activities of daily living (ADL). Each performance item is rated on this scale
 1193 with a given number of points assigned to each level or ranking. It uses ten
 1194 variables describing ADL and mobility. A higher number is associated with a
 1195 greater likelihood of being able to live at home with a degree of independence
 1196 following discharge from hospital.

1197

Category	Scale definition
Feeding	0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent
Bathing	0 = dependent 5 = independent (or in shower)
Grooming	0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)
Dressing	0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)
Bowels	0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent
Bladder	0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent
Toilet use	0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)
Transfers (bed to	0 = unable, no sitting balance

chair and back)	5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent
Mobility (on level surfaces)	0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards
Stairs	0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent

1198

1199

1200

1201 **13.2 Modified Rankin Scale (mRS)**

1202

1203 The modified Rankin Scale is a commonly used scale for measuring the
1204 degree of disability or dependence in the daily activities of people who have
1205 suffered a stroke or other causes of neurological disability. The addition of
1206 grade 6 indicates dead.

1207

Grade	Disability	Descriptions
0	No symptoms	No symptoms
1	No significant disability	Able to carry out all usual activities, despite some symptoms.
2	Slight disability	Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability	Requires some help, but able to walk unassisted.
4	Moderately severe disability	Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability	Requires constant nursing care and attention, bedridden, incontinent.
6	Dead	Dead

1208

1209

1210 **13.3 NIH Stroke Scale**

1211

1212 The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS)
 1213 is a tool used by healthcare providers to objectively quantify the impairment
 1214 caused by a stroke. The NIHSS is composed of 11 items, each of which
 1215 scores a specific ability between a 0 and 4. For each item, a score of 0
 1216 typically indicates normal function in that specific ability, while a higher score
 1217 is indicative of some level of impairment. The individual scores from each item
 1218 are summed in order to calculate a patient's total NIHSS score. The maximum
 1219 possible score is 42, with the minimum score being a 0.

1220

Instructions	Scale definition
<p>1a. Level of consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.</p>	<p>0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.</p>
<p>1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal</p>	<p>0 = Answers both correctly. 1 = Answers one correctly. 2 = Answers both incorrectly.</p>

cues.	
<p>1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.</p>	<p>0 = Performs both tasks correctly.</p> <p>1 = Performs one task correctly.</p> <p>2 = Performs neither task correctly.</p>
<p>2. Best gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve palsy (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.</p>	<p>0 = Normal.</p> <p>1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.</p> <p>2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.</p>

<p>3. Visual fields: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.</p>	<p>0 = No visual loss.</p> <p>1 = Partial hemianopia.</p> <p>2 = Complete hemianopia.</p> <p>3 = Bilateral hemianopia (blind including cortical blindness).</p>
<p>4. Facial palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.</p>	<p>0 = Normal symmetrical movements.</p> <p>1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling).</p> <p>2 = Partial paralysis (total or near-total paralysis of lower face).</p> <p>3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).</p>
<p>5. Arm motor: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not</p>	<p>0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds.</p> <p>1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.</p> <p>2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45)</p>

<p>noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.</p>	<p>degrees, drifts down to bed, but has some effort against gravity.</p> <p>3 = No effort against gravity; limb falls.</p> <p>4 = No movement. UN = Amputation or joint fusion, explain: _____</p> <p>5a. Left Arm</p> <p>5b. Right Arm</p>
<p>6. Leg motor: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.</p>	<p>0 = No drift; leg holds 30-degree position for full 5 seconds.</p> <p>1 = Drift; leg falls by the end of the 5-second period but does not hit bed.</p> <p>2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity.</p> <p>3 = No effort against gravity; leg falls to bed immediately.</p> <p>4 = No movement. UN = Amputation or joint fusion, explain: _____</p> <p>6a. Left Leg</p> <p>6b. Right Leg</p>
<p>7. Limb ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is</p>	<p>0 = Absent.</p> <p>1 = Present in one limb.</p> <p>2 = Present in two limbs.</p> <p>UN = Amputation or joint fusion, explain: _____</p>

<p>paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.</p>	
<p>8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.</p>	<p>0 = Normal; no sensory loss.</p> <p>1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched.</p> <p>2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.</p>
<p>9. Best language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from</p>	<p>0 = No aphasia; normal.</p> <p>1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided</p>

<p>responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.</p>	<p>materials, examiner can identify picture or naming card content from patient's response.</p> <p>2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.</p> <p>3 = Mute, global aphasia; no usable speech or auditory comprehension.</p>
<p>10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.</p>	<p>0 = Normal.</p> <p>1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty.</p> <p>2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.</p> <p>UN = Intubated or other physical barrier, explain: _____ _____</p>
<p>11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be</p>	<p>0 = No abnormality.</p> <p>1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.</p> <p>2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.</p>

taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	
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1227 **13.4 Mori Classification**

1228

1229 The Mori classification, formulated on the basis of DSA, delineates the length
1230 and geometry of intracranial stenosis as follows:

1231

Type	Descriptions
A	short (5 mm or less in length) concentric or moderately eccentric lesions less than totally occlusive
B	tubular (5 to 10 mm in length) extremely eccentric or totally occluded lesions, less than 3 months old
C	diffuse lesions (more than 10 mm in length), extremely angulated (>90°) lesions with excessive tortuosity of the proximal segment or totally occluded lesions, 3 months old or older

1232

1233

1234 **13.5 TICl perfusion categories**

1235

1236 The thrombolysis in cerebral infarction (TICl) grading system was described
 1237 as a tool for determining the response of thrombolytic therapy for ischemic
 1238 stroke. In interventional neuroradiology, it is commonly used for patients post
 1239 endovascular revascularization. Like most therapy response grading systems,
 1240 it predicts prognosis.

1241

Grade	Descriptions
0	No Perfusion. No antegrade flow beyond the point of occlusion.
1	Penetration With Minimal Perfusion. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.
2	Partial Perfusion. The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, e.g., the opposite cerebral artery or the arterial bed proximal to the obstruction.
2a	Only partial filling (<2/3) of the entire vascular territory is visualized.
2b	Complete filling of all of the expected vascular territory is visualized, but the filling is slower than normal.
3	Complete Perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.

1242

1243 **13.6 ASITN/SIR collateral flow grading system**

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1245 ASITN/SIR refers to American Society of Interventional and Therapeutic
1246 Neuroradiology/Society of Interventional Radiology (ASITN/SIR). The grading
1247 system scale is determined on DSA, classifying the cerebral collateral status
1248 ranging from grade 0 to 4. Grades 0-1, 2 and 3-4 are usually regarded as
1249 poor, moderate and good collateral flow.

1250

Grade	Descriptions
0	No collaterals visible to the ischemic site
1	Slow collaterals to the periphery of the ischemic site with persistence of some of the defect
2	Rapid collaterals to the periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory
3	Collaterals 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

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CASSISS TRIAL PROTOCOL

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THE CASSISS TRIAL

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1258 China Angioplasty & Stenting for Symptomatic Intracranial
1259 Severe Stenosis (CASSISS): A prospective, multi-center,
1260 randomized controlled trial

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1264

The CASSISS Trial

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Full Title	China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A prospective, multi-center, randomized controlled trial (RCT)
Short Title	The CASSISS Trial
Version	3.0
Date	May 1 st , 2015
Principal investigator	<i>Dr. Liqun Jiao</i> Department of Neurosurgery and Interventional Neuroradiology Xuanwu Hospital China International Neuroscience Institute Capital Medical University Beijing, China Email: liqunjiao@sina.cn Telephone: +86-10-83199060
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	<p><i>Dr. Long Yin</i> Tianjin Huanhu Hospital, Tianjin, China</p>
	<p><i>Dr. Shengping Huang</i> Guangdong Province Hospital of Traditional Chinese Medicine, Guangzhou, China</p>
Sponsor	Xuanwu Hospital, Capital Medical University
CRO	Tigermed Data Management Co., Ltd
Funding	Ministry of Health, People's Republic of China; Stryker Neurovascular Inc. (Fremont, CA, USA)

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1267

1268 **Protocol signature sheet**

Name	Signature	Date
<p>Department of Neurosurgery and Interventional Neuroradiology, China International Neuroscience Institute</p> <p>Xuanwu Hospital, Capital Medical University, Beijing, China</p>	Dr. Liqun Jiao	

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1351		

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1353 **1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

1354

AE	Adverse Event
AHA	American Heart Association
ALT	Alanine transaminase
APTT	Activated Partial Thromboplastin Time
ASA	American Stroke Association
ASITN/SIR	American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading System
AST	Aspartate aminotransferase
ATM	Atmosphere
BA	Basilar Artery
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
DSMB	Data Safety and Monitoring Board
DWI	Diffusion-weighted Imaging
ECG	Electrocardiogram
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
Cr	Creatine
CRF	Case Report Form
CRP	C-reactive protein
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTP	Computed Tomography Perfusion
DSA	Digital Subtraction Angiography
DAPT	Dural Anti-Platelet Therapy
DWI	Diffusion-Weighted Imaging
EC	Ethics Committee, synonymous to Institutional Review

	Board (IRB) and Independent Ethics Committee (IEC)
EDC	Electronic Data Capture
FAS	Full Analysis Set
FBG	Fasting blood glucose
FIB	Fibrinogen
GCP	Good Clinical Practice
HDL	High-density Lipoprotein
HbA1c	Glycated Hemoglobin
ICA	Internal Carotid Artery
ICAS	IntraCranial Atherosclerotic Stenosis
ICF	Informed Consent Form
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention To Treat
IVRS	Interactive Voice Response System
LDL	Low-density Lipoprotein
LOCF	Last Observed Carried Forward
MCA	Middle Cerebral Artery
MRA	Magnetic Resonance Angiography
mRS	Modified Rankin Scales
MTT	Mean Transit Time
NIHSS	National Institute of Health Stroke Scale
PI	Principle Investigator
PPS	Per-Protocol Set
PT	Prothrombin Time
PWI	Perfusion Weighted Imaging
RCT	Randomized Control Trial
PTAS	Percutaneous Transluminal Angioplasty and Stenting
SAE	Serious Adverse Event
SIT	Stroke In the Territory of symptomatic intracranial stenosis

Sponsor	The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.
TC	Total Cholesterol
TCD	TransCranial Doppler
TIA	Transient Ischemic Attack
TICI	Thrombolysis in Cerebral Infarction
TT	Thrombin Time
TTP	Time-to-Peak
USA	United States of America
VA	Vertebral Artery

1355

1356

1357 **2. SUMMARY**

1358

Title	China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A prospective, multi-center, randomized controlled trial
Objectives	To determine whether intracranial angioplasty and stenting with Gateway-Wingspan stent system adds benefit to medical therapy alone for preventing the primary outcomes (stroke or death within 30 days after enrollment, or stroke in the territory of the symptomatic intracranial artery between 30 days through 1 year in patients with recent TIA or stroke caused by 70% to 99% stenosis of a major intracranial artery).
Patient population	Patients with recent TIA or stroke caused by 70% to 99% stenosis of a major intracranial artery.
Sample size	380 (ratio 1:1)
Intervention	Complete randomization will be performed with an Interactive Voice Response System (Clinicalsoft Company, Beijing, China). Eligible patients will be randomized with a 1:1 ratio to medical therapy or medical therapy plus PTAS. Superiority is prospectively defined if the stenting arm has a significantly lower stroke or death rate.
Study design	prospective, multi-center, open-label, outcome-blinded, randomized controlled study.
Main parameters / Outcomes	<p>Primary outcomes:</p> <ul style="list-style-type: none"> Stroke or death within 30 days after enrollment, or stroke in the territory of the symptomatic intracranial artery (SIT) between 30 days and 1 year <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Disabling stroke or death after enrollment through 3 years in both arms; 2-year rate of the same-territory stroke;

	<ul style="list-style-type: none"> • 3-year rate of the same-territory stroke; • Any stroke, TIA, or cardiovascular events within a follow-up of 3 years. • Death rate in both arms within a follow-up of 3 years.
Follow-up schedule	Baseline, 30-day, 1-year, 2-year, and 3-year
Statistical analysis plan	<ul style="list-style-type: none"> • The primary and secondary outcomes including 2-year SIT and 3-year SIT will be compared between the groups using log-rank test by ITT. • For other secondary outcomes and baseline characteristics chi-square or Fisher exact test will be used for categorical variables, and t-test or Wilcoxon rank test for quantitative variables. • Kaplan-Meier curves will be used to show the incidence of outcomes over time. • All statistical tests will be performed by two-sided test. • A p-value <0.05 is considered statistically significant. • All analyses will be performed with SAS software, version 9.4 (SAS Institute, license: 11202165).

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1368 **3. INTRODUCTION AND RATIONALE**

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1370 **3.1 Description of the disease**

1371 Stroke is one of the leading causes of death in China and confers a large burden and
1372 effort upon patients and health professionals.¹⁻³ In contrast to Western countries,
1373 intracranial atherosclerotic stenosis (ICAS) is the most common vascular lesion in
1374 patients with cerebrovascular disease, and is an important cause of ischemic stroke
1375 and future recurrent events in China.⁴⁻⁷ Patients with ICAS have long been
1376 considered to be at high risk of recurrent stroke, which led to the development and
1377 wide use of percutaneous transluminal angioplasty and stenting (PTAS).⁸⁻¹²

1378

1379 **3.2 Description of the intervention**

1380 In 2005, the Wingspan Stent system (Stryker Neurovascular, Fremont, CA, USA)
1381 was approved under a Humanitarian Device Exemption by the US Food and Drug
1382 Administration (FDA), and had been used to reduce the rate of recurrent ischemic
1383 events among patients with severe symptomatic ICAS.¹³⁻¹⁷ However, the Stenting
1384 and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial
1385 Stenosis trial (SAMMPRIS trial, ClinicalTrials.gov number, NCT00576693), as the
1386 first RCT,¹⁸ demonstrated that aggressive medical management was superior to
1387 PTAS with the Wingspan stent among patients with symptomatic severe ICAS, both
1388 because the risk of early stroke after stenting was high (14.7%) and because the risk
1389 of stroke with aggressive medical therapy alone was lower than expected (5.8%).¹⁹

1390

1391 **3.3 Relevance for clinical practice**

1392 Since the SAMMPRIS trial, concerns have emerged that outcomes seen in a clinical
1393 trial setting may not be reproducible in non-RCT setting because of demonstrated
1394 more optimal surgical outcomes, less complication rates in high-volume centers, and
1395 good patient selection. The technical procedural problem rate, including guidewire-
1396 or angioplasty-related hemorrhage, could be minimized as more experienced
1397 operators overcome the learning curve for mastering the safety precautions of
1398 Wingspan stenting for ICAS.²⁰⁻²² In the post-SAMMPRIS era, several single or multi-
1399 center, registration studies in China,²³⁻²⁶ suggested lower risks of intracranial
1400 stenting for ICAS than those reported for SAMMPRIS.¹⁹

1401 Second, poor patient selection may increase the peri-operative risks and bias the
1402 outcome favoring medical treatment. In the stenting arm of the SAMMPRIS trial,
1403 more than 50% (115/224) of patients had a time interval from qualifying event to
1404 randomization of less than 7 days.¹⁹ Short interval or early stenting intervention may
1405 confer a higher risk of cerebral vascular event, including thromboembolic events,

1406 perforator stroke,²⁷ or even hemorrhagic transformation. Also, in the SAMMPRIS trial,
1407 22.8% of recruited patients had perforators stroke only, and those patients may not
1408 benefit from stenting in addition to medical therapy. Ideally, stenting may be
1409 considered for eligible patients based on poor collaterals and medical futility.²⁸

1410 Third, intracranial stenting involves a trade-off between a higher short-term
1411 perioperative risk in exchange for a lower long-term risk of stroke. In the SAMMPRIS
1412 trial the stenting group, mostly due to periprocedural complication, had more
1413 disabling or fatal stroke within 30 days than that in medical group (7.1% vs 1.8%),
1414 whereas the stenting group had less disabling or fatal stroke beyond 30 days than
1415 that in medical group (2.2% vs 6.2%).¹⁹

1416 The choice for ICAS treatment between medical therapy and stenting remains
1417 incompletely settled, at least for certain high-volume centers and for certain patient
1418 groups in a Chinese population. Furthermore, the recurrent stroke risk in the real
1419 world remains high despite maximal medical therapy.²⁹ Since the SAMMPRIS trial,
1420 an ever-increasing number of PTAS procedures surged beyond guidelines due to
1421 increased demand for ICAS treatment in China. The research community has
1422 maintained interest in tackling this important cause of stroke. Intracranial stenting
1423 with Wingspan is still awaiting a safe landing.^{30, 31}

1424

1425 **3.4 Hypothesis and rationale**

1426 It may be hypothesized that the clinical superiority observed in carefully selected
1427 patients in high-volume center who received medical therapy had diminished,
1428 making stenting a more favorable treatment strategy in comparison. As compared to
1429 the design of the SAMMPRIS trial, we thus feel that there is the need for a refined
1430 randomized trial reevaluating the role of stenting for ICAS. In the CASSISS trial,
1431 patients in both treatment groups have been followed up for 3 more years to
1432 establish whether early benefit in the medical group would persist over longer follow-
1433 up, or whether the medical group would have a high incidence of late stroke that
1434 would eliminate the early efficacy gap between groups.

1435

1436 **3.5 Objectives**

1437 **3.5.1 Primary objectives**

1438 To determine whether PTAS (using the Gateway PTA balloon catheter and
1439 Wingspan Stent System, Stryker, Fremont, CA, USA) combined with medical therapy
1440 is superior to medical therapy alone for preventing the primary outcome (stroke or
1441 death within 30 days after enrollment, or stroke in the territory of the symptomatic
1442 intracranial artery between 30 days through 1 year in patients with recent TIA or non-
1443 disabling stroke caused by 70% to 99% stenosis of a major intracranial artery).

1444

1445 3.5.2 Secondary objectives

1446 To compare outcomes between groups in terms of:

- 1447 • Disabling stroke or death after enrollment through 3 years in both arms;
- 1448 • 2-year rate of the same-territory stroke;
- 1449 • 3-year rate of the same-territory stroke;
- 1450 • Any stroke, TIA, or cardiovascular events within a follow-up of 3 years.
- 1451 • Death rate in both arms within a follow-up of 3 years.

1452

1453 4. STUDY DESIGN

1454 This trial is a prospective, multi-center, open-label, outcome-blinded, randomized
1455 control trial that will be conducted in 8 high-volume centers in China Mainland.
1456 Patients who meet inclusion criteria are randomized (1:1) to medical therapy alone or
1457 to PTAS plus medical therapy. This trial aims to enroll 380 cases. This sample size is
1458 large enough to result in acceptable data about safety and efficacy. At each
1459 investigational site, the local treating team will consist of at least a neurologist, a
1460 neurosurgeon, a neuroradiologist, and a research coordinator. The local treating
1461 team conducted enrollment after they reviewed the qualification of each patient.
1462 Patients assigned to the medical group will be discharged without further intervention.
1463 They will be administered aspirin 100 mg plus clopidogrel 75 mg per day for 90 days
1464 (aspirin or clopidogrel alone per day thereafter). Medical therapy will be identical in
1465 both arms and will be similar to the previously-described risk factor management for
1466 the SAMMPRIS trial and AHA/ASA guidelines.^{19 32} Patients assigned to the PTAS
1467 group will receive PTAS within 3-5 business days after enrollment. All patients will be
1468 followed-up in outpatient consultation or by telephone contact with the site
1469 investigators at 30-day, 1-year, 2-year, and 3-year marks until the last patient
1470 enrolled finishes 3-year follow-up or if patients die before the close-out visit (see flow
1471 chart).

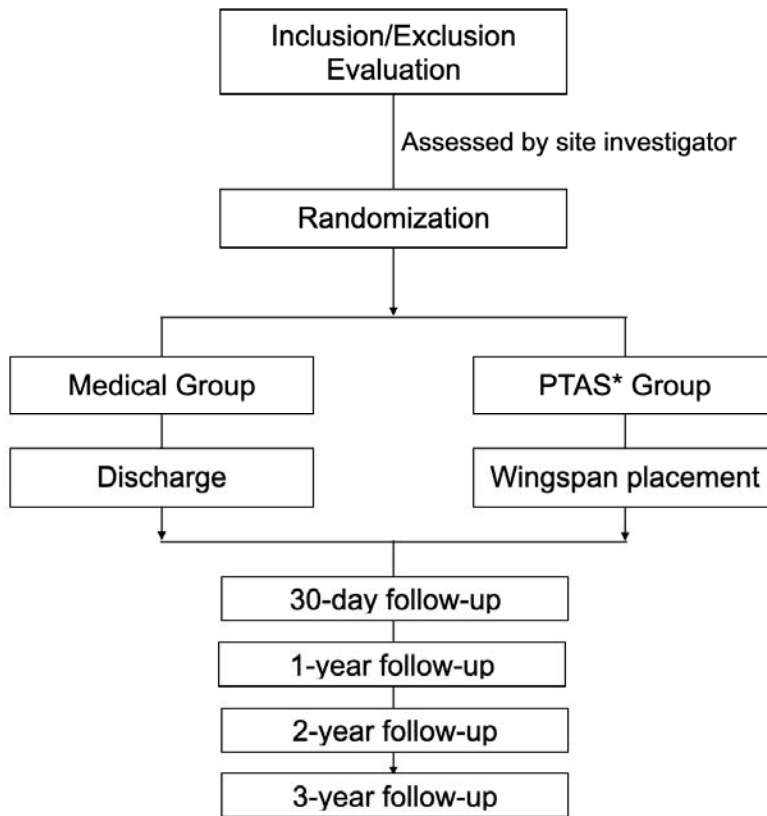
1472

1473 Expected enrollment initiation date: March, 2014

1474 Expected enrollment completion date: March, 2017

1475 Expected study end date: March, 2020

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Flow Chart

*PTAS, percutaneous transluminal angioplasty and stenting

1483 **5. STUDY POPULATION**

1484

1485 **5.1 Population**

1486 Patients with recent TIA or stroke caused by 70% to 99% stenosis of a major
 1487 intracranial artery. The stenotic degree will be determined on catheter angiogram
 1488 using the criteria of the Warfarin-Aspirin Symptomatic Intracranial Disease Study
 1489 [WASID].³³

1490

1491 **5.2 Credentialing of the participating centers and center eligibility**

1492 Centers are required to have a team consisting of a neurologist, a neurosurgeon, a
 1493 neuroradiologist, and a research coordinator. The randomized trial will not begin until
 1494 the clinical results of the participating centers have been certified. All the centers
 1495 who are interested in this trial will perform a competitive registration study of
 1496 recruiting a consecutive 100 PTAS as a pre-clinical trial within a duration of 8 to 10
 1497 months. Certification will be achieved by participating centers, whose clinical results
 1498 are audited by means of a validated selection process. Participating centers meet
 1499 the following criteria will be included in the randomized trial: 1) at least five cases
 1500 were performed by each primary operator during the lead-in phase; 2) annual
 1501 volume of intracranial PTAS procedures was more than 30 for the past three years
 1502 with a proven track record; and 3) according to the records of the past three years
 1503 30-day rate of stroke or death after PTAS in the territory of the qualifying artery was
 1504 lower than 15%.

1505 There will be 10 high-volume candidate sites (all tertiary hospitals), involved in a
 1506 competitive registration study of recruiting a combined total of 100 consecutive
 1507 patients treated with PTAS:

1508

Table: 10 candidate enrollment sites

#	Sites
1	Xuanwu Hospital, Capital Medical University, Beijing, China
2	The 1st Affiliated Hospital of Harbin Medical University, Harbin, China
3	Henan Provincial People's Hospital, Zhengzhou, China
4	Tangdu Hospital of Air Force Medical University, Xi'an, China
5	Beijing Hospital, Beijing, China
6	Qilu Hospital of Shandong University, Ji'nan, China
7	PLA Strategic support Force Characteristic Medical Center, Beijing,

	China
8	The 2nd affiliated Hospital of Guangzhou Medical University, Guangzhou, China
9	Tianjin Huanhu Hospital, Tianjin, China
10	Guangdong Province Hospital of Traditional Chinese Medicine, Guangzhou, China

1509

1510 **5.3 Inclusion criteria**

- 1511 1. Eligible patients aged between 30 and 80 years; intracranial arterial stenosis
 1512 related to the following non-atherosclerotic factors will be not be considered:
 1513 arterial dissection, moya-moya disease; vasculitic disease; herpes zoster,
 1514 varicella zoster or other viral vasculopathy; neurosyphilis; any other intracranial
 1515 infection; any intracranial stenosis associated with cerebrospinal fluid pleocytosis;
 1516 radiation-induced vasculopathy; fibromuscular dysplasia; sickle cell disease;
 1517 neurofibromatosis; benign angiopathy of central nervous system; postpartum
 1518 angiopathy; suspected vasospastic process, and suspected recanalized embolus;
- 1519 2. Symptomatic intracranial stenosis: presented with transient ischemic stroke (TIA)
 1520 or stroke within the past 12 months attributed to 70%-99% stenosis of a major
 1521 intracranial artery (ICA, MCA [M1], vertebral artery, or basilar artery [BA]);
- 1522 3. Degree of stenosis: 70%–99%; stenosis degree must be confirmed by catheter
 1523 angiography for enrollment in the trial;
- 1524 4. Remote infarctions on MRI scan, which can be accounted for by the occlusion of
 1525 the terminal cortical branches or hemodynamic compromise (perforator
 1526 occlusion excluded). Infarction due to perforators occlusion is defined as basal
 1527 ganglia or brainstem/thalamus infarction related with M1 or BA stenosis;
- 1528 5. Expected ability to deliver the stent to the lesion;
- 1529 6. All the patients should be performed with stenting beyond a duration of three
 1530 weeks from the latest ischemic symptom onset;
- 1531 7. No recent infarctions identified on MRI (indicated as high signals on DWI series)
 1532 upon enrollment;
- 1533 8. No massive cerebral infarction (>1/2 MCA territory), intracranial hemorrhage,
 1534 epidural or sub-dural hemorrhage, and intracranial brain tumor on CT or MRI
 1535 scan;
- 1536 9. mRS scale score of ≤ 2 ;

- 1537 10. Target vessel reference diameter must be measured to be 2.00 mm to 4.50 mm;
1538 target area of stenosis is ≤ 14 mm in length;
- 1539 11. No childbearing potential or has a negative pregnancy test within the past one
1540 week prior to study procedure; female patients had normal menses in the last 18
1541 months;
- 1542 12. Patient is willing and able to return for all follow-up visits required by the protocol;
- 1543 13. Patients understand the purpose and requirements of the study and have signed
1544 informed consent form.

1545

1546 **5.4 Exclusion criteria**

- 1547 1. Refractory to general anesthesia; not able to be overcome by pre-treatment with
1548 medical therapy
- 1549 2. Any condition that precludes proper angiographic assessment
- 1550 3. Tandem extracranial or intracranial stenosis (70%–99%) or occlusion that is
1551 proximal or distal to the target intracranial lesion
- 1552 4. Bilateral intracranial VA stenosis of 70%–99% and uncertainty about which lesion
1553 is symptomatic (for example, if patient has pon, midbrain, temporal and occipital
1554 symptoms)
- 1555 5. Presence of a previously placed intravascular stent or graft in the ipsilateral
1556 distribution within 30 days
- 1557 6. Previous treatment of target lesion with a stent, angioplasty, or other mechanical
1558 device, or plan to perform staged angioplasty followed by stenting of target
1559 lesion
- 1560 7. Severe vascular tortuosity or anatomy that would preclude the safe introduction
1561 of a guiding catheter, guiding sheath or stent placement
- 1562 8. Plan to perform concomitant angioplasty or stenting of an extracranial vessel
1563 tandem to an ipsilateral intracranial stenosis
- 1564 9. Presence of intraluminal thrombus proximal to or at the target lesion
- 1565 10. Any aneurysm proximal to or distal to intracranial stenotic artery
- 1566 11. Intracranial tumors or any intracranial vascular malformations
- 1567 12. Computed tomographic or angiographic evidence of severe calcification at target
1568 lesion
- 1569 13. Thrombolytic therapy within 24 hours before enrollment

- 1570 14. Evolving stroke or progressive neurologic signs within 24 hours before
1571 enrollment
- 1572 15. Stroke of sufficient size (>5 cm on CT or MRI) to place patient at risk of
1573 hemorrhagic transformation during the procedure; hemorrhagic transformation of
1574 an ischemic stroke within the past 15 days
- 1575 16. Previous spontaneous intracerebral (parenchymal) or other intracranial
1576 (subarachnoid, subdural, or epidural) hemorrhage within 30 days
- 1577 17. Untreated chronic subdural hematoma >5 mm in thickness
- 1578 18. Other cardiac sources of emboli such as left ventricular aneurysms, intracardiac
1579 filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcified
1580 aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal
1581 aneurysm, left atrial myxoma
- 1582 19. Myocardial infarction within previous 30 days
- 1583 20. Chronic atrial fibrillation; any episode of paroxysmal atrial fibrillation within the
1584 past six months, or history of paroxysmal atrial fibrillation requiring chronic
1585 anticoagulation
- 1586 21. Intolerance or allergic reaction to any of the medical therapy, including aspirin,
1587 clopidogrel, heparin, and local or general anesthetics
- 1588 22. History of life-threatening allergy to contrast medium. If not life threatening and
1589 can be effectively pre-treated, patient can be enrolled at physicians' discretion
- 1590 23. Recent gastrointestinal bleed that would interfere with antiplatelet therapy
- 1591 24. Active bleeding diathesis or coagulopathy; active peptic ulcer disease, major
1592 systemic hemorrhage within 30 days, active bleeding diathesis, platelets count
1593 <125,000, hematocrit <30, Hgb <10 g/dl, uncorrected INR >1.5, bleeding time >1
1594 minute beyond upper limit normal, or heparin-associated thrombocytopenia that
1595 increases the risk of bleeding, uncontrolled severe hypertension (systolic
1596 BP>180mm hg or diastolic BP>115mm hg), severe liver impairment (AST or 25.
1597 ALT >3 times normal, cirrhosis), creatinine >265.2 mmol/l (unless on dialysis).
1598 Major surgery (including open femoral, aortic, or carotid surgery) within previous
1599 30 days or planned in the next 90 days after enrollment
- 1600 25. Indication for warfarin or heparin beyond enrollment (exceptions allowed for use
1601 of systemic heparin during stenting procedure or subcutaneous heparin for deep
1602 venous thrombosis prophylaxis while hospitalized)
- 1603 26. Inability to understand and cooperate with study procedures or sign informed
1604 consent

- 1605 27. Severe dementia or psychiatric problems that prevent the patients from following
1606 an outpatient program reliably
- 1607 28. Pregnancy or of childbearing potential and unwilling to use contraception for the
1608 duration of this study
- 1609 29. Actively participating in another drug or device trial that has not completed the
1610 required protocol follow-up period
- 1611

1612 **6. Methods**

1613

1614 **6.1 Primary outcomes**

- 1615 • Stroke or death within 30 days after enrollment, or stroke in the territory of the
1616 symptomatic intracranial artery (SIT) between 30 days and 1 year

1617 **6.2 Secondary outcomes**

- 1618 • Disabling stroke or death after enrollment through 3 years in both arms;
1619 • 2-year rate of the same-territory stroke;
1620 • 3-year rate of the same-territory stroke;
1621 • Any stroke, TIA, or cardiovascular events within a follow-up of 3 years.
1622 • Death rate in both arms within a follow-up of 3 years.

1623

1624 **6.3 Definitions of outcomes**

- 1625 1. Stroke is defined as the rapid loss of brain functions due to disturbance in the
1626 blood supply to the brain that persists beyond 24 hours. Stroke is diagnosed by
1627 an independent outcome committee which is composed with experienced
1628 neurologists. They will collect additional key neuro-images (CT or MR scans) as
1629 adjunct evidence for outcome classification of ischemic or hemorrhagic stroke;
- 1630 2. Ischemic stroke is defined as a new focal neurological deficit of sudden onset
1631 lasting at least 24 hours that is not associated with a hemorrhage on brain CT or
1632 MRI. Ischemic strokes are further classified by the neurologic adjudicators as
1633 being either in or out of the territory of the qualifying artery;
- 1634 3. Hemorrhagic stroke is defined as parenchymal, sub-arachnoid, or intra-
1635 ventricular hemorrhage detected by CT or MRI that is associated with new
1636 neurological signs or symptoms lasting >24 hours or a seizure;
- 1637 4. Death, any of the following criteria:
- 1638 a) Procedure-related deaths, including those related to a complication of the
1639 procedure or treatment for a complication of the procedure.
- 1640 b) Death to due to cardiac cause, e.g., myocardial infarction, cardiac
1641 tamponade, and worsening heart failure
- 1642 c) Death of other cause (e.g., malignancy, trauma and suicide)
- 1643 d) Sudden or unwitnessed death
- 1644 e) Death of unknown cause

- 1645 5. Disabling stroke is defined by any of the following:
- 1646 a) a modified Rankin score of 3 or more, on a scale of 0 to 6, with higher
1647 scores indicating greater disability;
- 1648 b) an increase in at least one mRS category from an individual's pre-stroke
1649 baseline
- 1650 c) a score on the composite National Institutes of Health Stroke Scale
1651 (NIHSS) of 7 or more, on a scale of 0 to 42, with higher scores indicating
1652 more severe deficits;
- 1653 d) an increase in at least 4 NIHSS scales from pre-stroke baseline.
- 1654 6. Complication rates associated with stenting procedures: refer perforator
1655 occlusion, guidewire perforation, artery-to-artery embolism, stent thrombosis, or
1656 reperfusion hemorrhage within 72 hours after PTAS procedures.
- 1657 7. Restenosis rate: if patients have follow-up vascular imaging, the imaging
1658 modality will be recorded, in addition to the percent stenosis of the target lesion.
1659 Re-stenosis is defined as 50% narrowing or greater irrespective of symptoms.
- 1660 8. TIA: duration of a focal or global neurological deficit <24 h, any variable
1661 neuroimaging does not demonstrate a new hemorrhage or infarction;
- 1662 9. Cardiovascular events: refer a class of events that is related to stenting or
1663 medical therapy, which includes coronary artery diseases (CAD) such as angina
1664 and myocardial infarction.
- 1665 10. BI, mRS and NIHSS: please refer the Appendix 13.1, Appendix 13.2 and
1666 Appendix 13.3.
- 1667 11. Compliance of drug: patients will be contacted at 30-day, 1-year, 2-year and 3-
1668 year after enrollment, to gather information regarding the use of anti-platelet
1669 drugs, changes in prescribed drugs, medical condition and quality of life.
- 1670 a) very good, 80% - 120%;
- 1671 b) good, 60% - 79%;
- 1672 c) fair, 40% - 59%;
- 1673 d) poor, < 40%.
- 1674
- 1675
- 1676
- 1677

1678 **6.4 Definitions of other parameters**

1679 6.4.1 Major vascular complications

- 1680 1. Non-neurovascular death: e.g., trauma, suicide, malignancy, or cardiovascular
1681 mortality;
- 1682 2. Major vascular complication: e.g., aortic dissection, aortic rupture, or annulus
1683 rupture;
- 1684 3. Access site of access-related vascular injury (dissection, stenosis, perforation,
1685 rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve
1686 injury, or percutaneous closure device failure) leading to death, life-threatening
1687 or major bleeding, or neurological impairment;
- 1688 4. Distal cerebral embolism from a vascular source requiring surgery or
1689 endovascular intervention or irreversible neurological damage;
- 1690 5. Any new ipsilateral lower extremity ischemia documented by patient symptoms,
1691 physical examination, and/or decreased or absent blood flow on lower extremity
1692 angiogram;
- 1693 6. surgery for access site-related nerve injury;
- 1694 7. permanent access site-related nerve injury.

1695

1696 6.4.2 Minor vascular complications

- 1697 1. Access site of access-related vascular injury (dissection, stenosis, perforation,
1698 rupture, arteriovenous fistula, pseudoaneurysm, hematoma, or percutaneous
1699 closure device failure) not leading to death, life-threatening or major bleeding, or
1700 neurological impairment;
- 1701 2. Distal cerebral embolism treated with mechanical thrombectomy not resulting in
1702 irreversible neurological damage;
- 1703 3. Any unplanned endovascular stenting or surgical intervention not meeting the
1704 criteria for a major vascular complication;
- 1705 4. Vascular repair: e.g., ultrasound-guided compression or injection embolization,
1706 transcatheter embolization or stent-graft;
- 1707 5. Percutaneous closure device failure.

1708

1709 **6.5 Treatment assignment**

1710 Eligible patients will be enrolled with their baseline data entered into a web-based
1711 database system. Patients will be randomized (1:1) to medical therapy alone or
1712 medical therapy plus stenting using Wingspan. Randomized outcomes will not be
1713 blinded to the patients and their family. When a patient is included for participation,
1714 site investigator will be informed. The patients will be excluded from the ITT analysis
1715 if they sign the ICF while they are not confirmed eligible with central adjudication.

1716 A summary will be made of patients who are randomized to PTAS group but do not
1717 undergo surgery, and the patients who are randomized to medical therapy but
1718 receive surgery. Compliance will be assessed by the investigator at each visit using
1719 information provided by the care-giver or patients themselves. This information
1720 should be recorded in the source document at each visit.

1721

1722 **6.6 Randomization and numbering**

1723 Complete randomization will be performed with an Interactive Voice Response
1724 System (Clinicalsoft Company Limited, Beijing, China; <http://ivr.clinicalsoft.cn>).
1725 Eligible patients will be randomized with a 1:1 ratio to medical therapy or medical
1726 therapy plus PTAS. Each patient has its unique ID number (center number plus
1727 screening order number) in this trial. This center number will be assigned to each
1728 participating center. Once the patients or their legal representatives sign the
1729 informed consent form (ICF) at each center, they will be assigned with a screening
1730 order number. At each center, the screening order number will be in order of the
1731 patients' enrollment (e.g., 001, 002, 003 and so on).

1732

1733 **6.7 Medical group**

1734 Patients randomized to medical group will received medical therapy and be
1735 discharged without further intervention.

1736

1737 **6.7.1 Medical therapy**

1738 Medical therapy will be identical in both arms and will be similar to the previously
1739 described risk factor management for the SAMMPRIS trial. In brief, it includes both
1740 aspirin 100 mg plus clopidogrel 75 mg per day for 90 days (aspirin 100 mg or
1741 clopidogrel 75mg alone per day thereafter) and management of risk factors.

1742 The drugs used in the trial are commercially available in China. Several generic
1743 aspirin or clopidogrel are available and allowed to be used. Medical therapy regimen,
1744 including DAPT and statin will be purchased by the patients or their family member,

1745 who later received various degrees of reimbursement from the Chinese social
1746 security system.

1747

1748 6.7.2 Management of risk factors

1749 Risk factor control is based on the AHA/ASA guidelines³² and the SAMMPRIS¹⁹ trial
1750 protocol. Medical management of risk factors consists of normalizing low-density
1751 lipoprotein (LDL-C) (statins, target LDL-C <2.58 mmol/l [100 mg/dl]), hypertension
1752 (systolic pressure <140 mmHg and a diastolic pressure <90 mmHg), glucose
1753 disorder (in diabetic patients, hemoglobin A1c [HbA1c] will be checked at enrollment
1754 and during each clinical visit with a target level of <6.5%), and lifestyle modification.
1755 Intensive management of risk factors is applicable to all the included patients (e.g.,
1756 hypertension, lipid disorder, diabetes mellitus, overweight, obesity, physical inactivity,
1757 and cigarette smoking).

1758

1759 6.7.3 Health education and lifestyle modification

- 1760 1. Health education and lifestyle modification: quit smoking, moderate-intensity
1761 physical exercises (at least 3 times per week for 30 min per session).
- 1762 2. Obesity: BMI should be maintained below 25 kg/m². Weight reduction is
1763 associated with a lowering in BP and may thereby reduce stroke risk.

1764

1765

1766 **6.8 PTAS group**

1767 Patients randomized to PTAS group are to be scheduled for surgery within 3-5
1768 business days after enrollment. The study protocol requires that the stenting
1769 procedure be performed by a qualified operator at each site.

1770

1771 6.8.1 PTAS procedure

1772 Patients randomized to stenting will be placed on DAPT (aspirin, 100 mg daily and
1773 clopidogrel 75 mg daily) for 3-5 consecutive days before the procedure. No loading
1774 dose will be allowed. The study protocol requires that the PTAS procedure is
1775 typically performed under general anesthesia by a credentialed interventionist who
1776 should be the primary operator. The procedure is typically performed via a
1777 transfemorally placed 6F-long sheath or guiding catheter. The stenotic lesion is
1778 primarily crossed with a standard 0.014" microcatheter microwire system under high
1779 magnification fluoroscopic roadmap control. Once across the lesion, the
1780 microcatheter is exchanged over a 300-cm, 0.014" microwire for a Gateway balloon

1781 catheter. After angioplasty, the balloon catheter is exchanged for a Wingspan stent
1782 delivery system and the self-expanding Wingspan stent is deployed across the
1783 stenosis. If the residual stenosis after inserting the Wingspan stent is >50%, the
1784 study protocol allows for postdilation with a new balloon catheter. The protocol
1785 required frequent measurements of blood pressure during the procedure and at least
1786 1 measurement every half an hour during the next 24 hours while the patient is
1787 monitored. The patient will be continued on aspirin, 100 mg daily, and clopidogrel, 75
1788 mg daily, for the next 90 days and subsequently on aspirin or clopidogrel alone. Risk
1789 factor control should be applied thereafter.

1790

1791 6.8.2 Rescue therapy for PTAS

- 1792 1. If the residual stenosis is >50% after the primary Wingspan placement, study
1793 protocol allows for the postdilation with a new balloon catheter to achieve better
1794 angioplasty outcome.
- 1795 2. If the initial Wingspan stent could not be delivered to the target lesion, the
1796 interventionalist can try to deliver a second Wingspan stent.
- 1797 3. If the second Wingspan stent cannot be delivered to the target lesion, the
1798 interventionalist has the following options: a) angioplasty alone; b) using non-
1799 study stents; c) procedure aborted.
- 1800 4. If an ischemic stroke occurs or an intraluminal thrombus develops during the
1801 procedure, the interventionalist or stroke neurologist (if available) should
1802 administrate appropriate treatment. This may include intravenous or intraarterial
1803 use of thrombolytic therapy, e.g., glycoprotein IIb-IIIa Inhibitor (Tirofiban).
- 1804 5. If a major dissection, other occlusive complication, or stent misplacement occurs
1805 that requires placement of a second Wingspan stent, this may be done as a
1806 rescue procedure. In the meantime, neuro ICU will provide reservations to deal
1807 with patients with serious complications.

1808

1809 6.9 Follow-up schedule

1810 Clinical assessment of patients will be conducted in outpatient consultation or by
1811 telephone contact with the site investigators at 30-day, 1-year, 2-year, and 3-year or
1812 if the patients died before the close-out visit. At each follow-up visit, patients will be
1813 examined by study physicians who also manage the patients' vascular risk factors.
1814 Imaging assessment will be achieved by head MRI, CTA, MRA, or DSA at each visit
1815 if possible.

1816

1817

Table: follow-up schedule

	In-hospital			Follow-up (Paper-based CRF)			
	Baseline	Procedure	Discharge	30- day	1- year	2- year	3- year
ICF	<input checked="" type="checkbox"/>						
In-/Exclusion criteria	<input checked="" type="checkbox"/>						
Demographics	<input checked="" type="checkbox"/>						
Medical history	<input checked="" type="checkbox"/>						
Physical exam	<input checked="" type="checkbox"/>			<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Neurological status							
NIHSS	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
mRS	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Barthel Index	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Lab test	<input checked="" type="checkbox"/>				<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Neuro-imaging							
CT/MRI (DWI)	<input checked="" type="checkbox"/>				<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
TCD/CTA/MRA	<input checked="" type="checkbox"/>				<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
CTP/PWI	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>			<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
DSA	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>			<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Medication	<input checked="" type="checkbox"/>			<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
AE/SAE		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

1818

1819

1820 6.9.1 Baseline

1821 At baseline, the following parameters should be documented:

1822 I. Date of ICF

1823 II. Demographics

1824 III. Medical history

1825 a. Present history

1826 b. Previous history, e.g., hypertension, diabetes, lipid disorder, coronary
1827 and peripheral artery diseases, smoking and alcohol abuse, etc.

1828 IV. Clinical status

1829 a. Physical examination

1830 b. Vital signs: blood pressure, pulse rate, respiratory rate and body
1831 temperature

1832 c. ECG

1833 d. BMI

1834 V. Neurological status

1835 a. NIHSS

1836 b. mRS

- 1837 c. Barthel Index
- 1838 VI. Lab test
- 1839 a. Routine blood test
- 1840 b. Liver function: e.g., ALT, AST, etc.
- 1841 c. Renal function: e.g., Cr, BUN, etc.
- 1842 d. Renal damage: proteinuria (according to site's preference and facilities)
- 1843 e. FBG and HbA1c
- 1844 f. Lipid level: LDL, HDL and TC
- 1845 g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.
- 1846 h. Inflammation markers: CRP
- 1847 i. Pregnancy test
- 1848 VII. Neuro-imaging
- 1849 a. Cranial CT/MR (DWI)
- 1850 b. TCD/CTA/MRA
- 1851 c. CTP/PWI parameters: CBF, CBV, MTT and TTP
- 1852 d. DSA
- 1853
- 1854 6.9.2 Procedure (for PTAS group)
- 1855 During the procedure, the following parameters should be documented:
- 1856 I. Date of the procedure
- 1857 a. delayed procedure: beyond 5 business day after enrollment
- 1858 b. procedure on time: within 5 business day after enrollment
- 1859 II. Operator of the procedure
- 1860 III. Anesthesia: general or local
- 1861 IV. Morphological characteristics of the lesion on DSA
- 1862 a. side: right or left
- 1863 b. size: diameter and length (mm)
- 1864 c. location: M1, BA, ICA or VA
- 1865 d. stenotic degree (%) determined using the WASID criterion³³
- 1866 e. Mori classification: type A, B or C³⁴ (Appendix 13.4)

- 1867 f. TICI perfusion categories³⁵ (Appendix 13.5)
- 1868 g. ASITN/SIR collateral flow grading system³⁵ (Appendix 13.6)
- 1869 V. Type of procedures
- 1870 a. angioplasty plus stent placement
- 1871 b. angioplasty alone
- 1872 c. none
- 1873 VI. Angioplasty balloon
- 1874 a. size: diameter and length (mm)
- 1875 b. type: Gateway or others
- 1876 c. number: 1 or more
- 1877 d. inflation pressure (atm)
- 1878 VII. Stent delivered
- 1879 a. size: diameter and length (mm)
- 1880 b. type: Wingspan or others
- 1881 c. number: 1 or more
- 1882 VIII. Residual stenosis (%)
- 1883 IX. Use of post-dilation:
- 1884 a. yes or no
- 1885 b. if yes, type and size of the balloon used
- 1886 c. inflation pressure (atm)
- 1887 d. residual stenosis after post-dilation
- 1888 X. Rescue therapy
- 1889 XI. Post-PTAS neurological status
- 1890 a. NIHSS
- 1891 b. mRS
- 1892 c. Barthel Index
- 1893 XII. AE/SAE
- 1894
- 1895 6.9.3 Discharge
- 1896 Before discharge, the following parameters should be documented:

1897 I. Neurological status

1898 a. NIHSS

1899 b. mRS

1900 c. Barthel Index

1901 II. AE/SAE

1902

1903 6.9.4 30-day follow-up

1904 At 30-day follow-up, the following parameters should be documented:

1905 I. Clinical status

1906 a. Physical examination

1907 b. Vital signs: blood pressure, pulse rate, respiratory rate and body
1908 temperature

1909 c. ECG

1910 d. BMI

1911 II. Neurological status

1912 a. NIHSS

1913 b. mRS

1914 c. Barthel Index

1915 III. Medication

1916 IV. AE/SAE

1917

1918 6.9.5 1-year follow-up

1919 At 1-year follow-up, the following parameters should be documented:

1920 I. Clinical status

1921 a. Physical examination

1922 b. Vital signs: blood pressure, pulse rate, respiratory rate and body
1923 temperature

1924 c. ECG

1925 d. BMI

1926 II. Neurological status

1927 a. NIHSS

- 1928 b. mRS
- 1929 c. Barthel Index
- 1930 III. Lab test
- 1931 a. Routine blood test
- 1932 b. Liver function: e.g., ALT, AST, etc.
- 1933 c. Renal function: e.g., Cr, BUN, etc.
- 1934 d. Renal damage: proteinuria (according to site's preference and facilities)
- 1935 e. FBG and HbA1c
- 1936 f. Lipid level: LDL, HDL and TC
- 1937 g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.
- 1938 h. Inflammation markers: CRP
- 1939 IV. Neuro-imaging
- 1940 a. Cranial CT/MR (DWI)
- 1941 b. TCD/CTA/MRA
- 1942 c. CTP/PWI parameters: CBF, CBV, MTT and TTP
- 1943 d. DSA
- 1944 V. Medication
- 1945 VI. AE/SAE
- 1946
- 1947 6.9.6 2-year follow-up
- 1948 At 2-year follow-up, the following parameters should be documented:
- 1949 I. Clinical status
- 1950 a. Physical examination
- 1951 b. Vital signs: blood pressure, pulse rate, respiratory rate and body
- 1952 temperature
- 1953 c. ECG
- 1954 d. BMI
- 1955 II. Neurological status
- 1956 a. NIHSS
- 1957 b. mRS

- 1958 c. Barthel Index
- 1959 III. Lab test
- 1960 a. Routine blood test
- 1961 b. Liver function: e.g., ALT, AST, etc.
- 1962 c. Renal function: e.g., Cr, BUN, etc.
- 1963 d. Renal damage: proteinuria (according to site's preference and facilities)
- 1964 e. FBG and HbA1c
- 1965 f. Lipid level: LDL, HDL and TC
- 1966 g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.
- 1967 h. Inflammation markers: CRP
- 1968 IV. Neuro-imaging
- 1969 a. Cranial CT/MR (DWI)
- 1970 b. TCD/CTA/MRA
- 1971 c. CTP/PWI parameters: CBF, CBV, MTT and TTP
- 1972 d. DSA
- 1973 V. Medication
- 1974 VI. AE/SAE
- 1975
- 1976 6.9.7 3-year follow-up
- 1977 The following parameters should be documented:
- 1978 I. Clinical status
- 1979 a. Physical examination
- 1980 b. Vital signs: blood pressure, pulse rate, respiratory rate and body
- 1981 temperature
- 1982 c. ECG
- 1983 d. BMI
- 1984 II. Neurological status
- 1985 a. NIHSS
- 1986 b. mRS
- 1987 c. Barthel Index

- 1988 III. Lab test
- 1989 a. Routine blood test
- 1990 b. Liver function: e.g., ALT, AST, etc.
- 1991 c. Renal function: e.g., Cr, BUN, etc.
- 1992 d. Renal damage: proteinuria (according to site's preference and facilities)
- 1993 e. FBG and HbA1c
- 1994 f. Lipid level: LDL, HDL and TC
- 1995 g. Blood coagulation test: APTT, PT, TT, FIB, INR, etc.
- 1996 h. Inflammation markers: CRP
- 1997 IV. Neuro-imaging
- 1998 a. Cranial CT/MR (DWI)
- 1999 b. TCD/CTA/MRA
- 2000 c. CTP/PWI parameters: CBF, CBV, MTT and TTP
- 2001 d. DSA
- 2002 V. Medication
- 2003 VI. AE/SAE
- 2004
- 2005 **6.10 Consent withdrawal**
- 2006 Patients may voluntarily withdraw consent to participate in the study for any reason
- 2007 at any time. Consent withdrawal occurs only when a patient: 1) does not want to
- 2008 participate in the study anymore; 2) or does not want any further visits or
- 2009 assessments; 3) or does not want any further study-related contacts.
- 2010 When a patient withdraws consent, the investigator is required to determine the
- 2011 primary reason for this decision and record this information. Further attempts to
- 2012 contact the patient are not allowed unless safety efficacy require follow-up. After
- 2013 withdrawal, patients will not be replaced by others and their randomized ID number
- 2014 will not be re-used.
- 2015
- 2016 **6.11 Follow-up of subjects withdrawn from treatment assignment**
- 2017 Some cases may withdraw from treatment assignment. Since the statistical analysis
- 2018 is planned for ITT principle, they will be analyzed in the group that they were
- 2019 originally allocated to.

2020

2021 6.12 Lost for follow-up

2022 For patients whose status are unclear because they fail to appear for study visits
2023 without stating an intention to withdraw, the investigator should show "due diligence"
2024 by contacting the patient, family or family physician as agreed in ICF and by
2025 documenting in the source documents steps taken to contact the patient, e.g., dates
2026 of telephone calls, registered letters, etc. Lost for follow-up could be accounted by no
2027 reply although try to contact the cases three times or more. A patient should not be
2028 formally considered lost to follow-up until his/her scheduled end of study visit would
2029 have occurred.

2030

2031 6.13 Study completion and post-study treatment

2032 At the end of the study visit, the investigator should provide follow-up medical care
2033 for all patients who are prematurely withdrawn from the study or refer them for
2034 appropriate ongoing care. When the patient has completed all scheduled study
2035 assessments, the investigator is required to inform to record the patient completion
2036 in the EDC system.

2037

2038 6.14 Premature termination of the study

2039 During the trial, AEs or SAEs will be reported to DSMB. The DSMB will monitor
2040 SAEs, major safety events, device and procedure failures and any device-related
2041 adverse events. In the current trial, SAEs mainly refer disabling stroke, symptomatic
2042 intracranial hemorrhage or death within 1 year after enrollment and all-cause death
2043 within a follow-up 3 years. The stopping rules will be developed by DSMB and the
2044 advices of DSMB will be sent to the executive and steering committee of the study.
2045 The Executive and Steering Committee will be responsible for informing the EC
2046 whether the advices are fully implemented or not.

2047

2048 6.15 Outcome assessment

2049 This is a multicenter phase IV RCT with open-label treatment and blinded outcome
2050 assessment. Outcome assessment will be sent to an independent Outcome
2051 Committee. The committee is composed of experienced neurologists who are not
2052 involved in the study, will be blinded to the treatment assignment. All the outcome
2053 will be adjudicated by the outcome committee, and a consensus will be reached by a
2054 third clinician in case of discrepancies.

2055

2056 **7. SAFETY MONITORING**

2057 **7.1 Adverse events (AE)**

2058 AE is defined as any unfavorable and unintended sign, symptom or disease that
2059 occurs to a subject while enrolled in a clinical investigation, whether or not
2060 considered related to the study intervention or device. Medical conditions that exist
2061 at study enrollment are not considered an AE unless condition worsens after use of
2062 the study intervention or device.

2063

2064 **7.2 Serious adverse events (SAE)**

2065 7.2.1 Definition of SAE

2066 A SAE is any medical experience regardless of its relationship to the investigational
2067 device or study devices that occurs during subject enrollment in this trial that results
2068 in any of the following:

- 2069 ☞ need to be hospitalized or prolonged hospitalization;
- 2070 ☞ persistent or significant disability/incapacity;
- 2071 ☞ death of the study subject;
- 2072 ☞ necessitates an intervention to prevent a permanent impairment of a body
2073 function or permanent damage to a body structure
- 2074 ☞ or causing congenital anomalies/birth defects.

2075

2076 7.2.2 SAE reporting

2077 All SAEs will be recorded in the table of CRF. The details of the SAEs, including
2078 starting time, ending time, duration, treatment, outcome, and the relationship with
2079 intervention will be recorded as well. Frequency of SAEs will be summarized
2080 according to the assignments. All recorded AEs/SAEs will be reported to the
2081 investigator. SAEs that result in death or life-threatening stroke will be reported to
2082 DSMB/EC within 14 days after the investigator is informed for the first time. In the
2083 current trial, SAEs mainly refer disabling stroke, symptomatic intracranial
2084 hemorrhage or death within 1 year after enrollment and all-cause death within a
2085 follow-up 3 years. For safety analysis, an independent summary will list SAEs related
2086 to intervention in PTAS group.

2087

2088 7.2.3 Management and follow-up of AEs/SAEs

2089 Investigators should take appropriate treatment for AEs to ensure the safety of
2090 patients and track all AEs/SAEs until they are properly resolved, or the condition is

2091 stable. Additional medical procedures and/or referral to a medical specialist may be
2092 required to confirm whether the patients are qualified to continue to participate in the
2093 study.

2094

2095 **8. DATA MANAGEMENT**

2096 **8.1 Study Data Collection**

2097 Site coordinator records data by filling out the paper-based CRFs for each case. The
2098 sponsor (Beijing Xuanwu Hospital) provides CRFs to each site. Site investigator is
2099 responsible for that all CRFs are completed, reviewed, and approved. Also, site
2100 investigator will sign on CRFs and confirm that clinical, imaging and laboratory data
2101 entered into the CRFs are true.

2102 Patient ID in CRFs should be recorded in an anonymous form, which are only
2103 identified by the patient ID number and Chinese phonetic alphabets (pinyin) initials.
2104 CRFs should be filled in with a black ballpen based on the original document. Fill in
2105 “not done” for missing data; fill in “not applicable” if not applicable; fill in “unknown”
2106 for unknown data.

2107 If the data entered into CRFs needs to be revised, cross out the error with a single
2108 line so that it can still be seen clearly, and then fill in the correct data next to it. The
2109 revisions should be approved and signed by the site investigator. If necessary, the
2110 reason for the revisions should be indicated. Site investigator will review the integrity
2111 and accuracy of the CRFs and make further corrections and amendments if
2112 necessary. When the trial is finished, site investigator will send the CRFs to
2113 Tigermed Data Management Co., Ltd; (<https://tigermedgrp.com>) for data entry.

2114 The data in the paper-based CRFs will be entered into the database by Tigermed
2115 Data Management Co., Ltd, with its completeness and accuracy reviewed. The
2116 missing data and questioned data are reported in the data query form, which will be
2117 sent back to the site investigator for further verification. Site investigator will send
2118 back in the resolved query form with signature and date of signing. Tigermed Data
2119 Management shall be responsible for entering the resolved results into the database.
2120 After the final confirmation is completed and all queries are resolved, the database is
2121 updated and locked. Data is transferred from the database directly to the data file
2122 (SAS data set) for statistical analysis. The data can be changed after database is
2123 unlocked upon reasonable request.

2124

2125 **8.2 Data Processing and Quality Control**

2126 The data entry is performed by the staff trained by Tigermed Data Management Co.,
2127 Ltd. All the input data should go through verification and range check. The staff will
2128 be notified of a possible error, depending on the data validation. The staff will not
2129 move on unless the error is resolved.

2130 All CRFs will be subject to preliminary inspection for data missing, inconsistency and
2131 deviation. Data inconsistency will be completed by electronic tracking and resolved
2132 by site coordinators and investigators.

2133

2134 Each data input will receive regular cross-check within forms. Site coordinators will
2135 be informed in case of errors identified. Corrections to the data in CRFs will be made
2136 by the site coordinators, and approved by the site investigators.

2137

2138 The data editing will continue when all data is cleaned. The site coordinators will
2139 supervise the verification of on-site source documents. If further data related to the
2140 source file is found during the site visit, additional queries will be generated and
2141 processed by the site coordinators.

2142

2143 **8.3 Data storage**

2144 The investigator will document adequate records during the conduct of the study.
2145 Trial data including patient files, CRFs, ICFs, original copies of results, and imaging
2146 outcome, will be kept on files by the investigator for a period of 10 years or more.

2147

2148

2149 **9. STATISTICAL ANALYSIS**

2150 **9.1 Analysis data set**

2151 Full Analysis Set (FAS): all the subjects who are randomized into groups will be
2152 included. Subjects who do not meet the eligible criteria or who withdraw immediately
2153 after randomization without receiving any interventions will be excluded. According to
2154 the intention-to-treat (ITT) principle, all randomized patients will be analyzed
2155 according to the treatment group assigned to them at the time of randomization. All
2156 presenting analyses will be conducted in the FAS population unless otherwise
2157 specified

2158 Per-protocol Set (PPS): PPS refers population who are treated according to the
2159 study protocol, e.g., fulfilling eligibility criteria, assigned treatment after randomization,
2160 medication and follow-up protocol, and completion of the case report form). PPS
2161 analysis was conducted on the population who had not crossovers between groups
2162 or significant protocol violations. Crossover population from one arm to the other will
2163 not impact the ITT analysis. For PTAS group, significant protocol violations include: 1)
2164 use of non-study stents; 2) delayed procedure of PTAS (beyond 5 business days
2165 after enrollment; 3) procedure is aborted before lesion is accessed; 4) procedure is
2166 aborted due to total occlusion; 5) receive angioplasty only and others.

2167 For other details, please refer to the Statistical Analysis Protocol (SAP) in the
2168 Appendix.

2169

2170 **9.2 Analysis close date**

2171 The analysis close date for each arm is at the completion of 3-year follow-up of the
2172 last enrolled patient. The primary outcome is based on the exact 3-year time point for
2173 each patient, and event.

2174

2175 **9.3 Sample size calculation**

2176 For symptomatic severe (70-99%) intracranial atherosclerotic stenosis, 1 year of
2177 ipsilateral stroke risk in medical therapy group WASID study was 18%,³⁶ which was
2178 7.3% in a study by the Wingspan stent therapy.²³ At a significance level of 5% on
2179 both sides, the absolute difference of 10.7% (relative risk reduction 59%), and a
2180 power of 80%, within 12 months of follow-up, a total of 302 patients need to be
2181 evaluated. Assuming a 20% incidence of loss of follow-up and/or withdrawal, a total
2182 of 380 patients, 190 in the stent group and 190 in the medical group, are required to
2183 be enrolled in this study.

2184

2185 **10. STUDY COMMITTEES**

2186 **10.1 Executive and Steering Committee**

2187 Executive committee is composed of principle and site investigators from the
2188 participating centers, which is responsible for making decisions about the direction
2189 and strategy of the trial. During the trial period, this committee fulfills the coordination,
2190 implementation, organize regular meeting, and report progress. Also, it is required to
2191 review main trial publications, analysis plan and publication policy, and consider
2192 recommendations of DSMB.

2193

2194 **10.2 Ethics Committee**

2195 The trial should first obtain the written approval from the Ethics committee of Xuanwu
2196 Hospital, Capital Medical University, Beijing, China. The trial will not enroll patient
2197 until the study protocol is approved by the local ethics committee (EC) in the other
2198 sites. In case of any major amendments to the trial protocol, renewed written
2199 approval should be obtained from the ethics committee. Updated ICF after
2200 amendments will be sent to patients in the active period of the trial. Minor
2201 amendments will not be sent to EC.

2202

2203 **10.3 Data and safety Monitoring Board (DSMB)**

2204 An independent DSMB that is composed of neurologist, neurosurgeon,
2205 neuroradiologist and biostatistics experts who are not involved in the conduct of the
2206 trial. DSMB members should not have any scientific or financial conflicts of interest
2207 with the sponsor or investigator. DSMB is responsible for study conduct, progress
2208 and efficacy. By reviewing safety data, DSMB will advise executive committee to
2209 continue, modify or terminate the trial early.

2210

2211 **10.4 Clinical outcome committee**

2212 Clinical outcome assessment will be sent to an independent Outcome Committee.
2213 The committee composed of experienced neurologists who are not involved in the
2214 study, will be blinded to the treatment assignment. All the outcomes will be
2215 adjudicated by the outcome committee, and a consensus will be reached by a third
2216 clinician in case of discrepancies. For details, please refer to *2.9 Assessments of*
2217 *clinical outcome* in the *2. Supplementary Methods*.

2218

2219 **10.5 Imaging outcome committee:**

2220 An independent imaging core-lab, IsCore Image CoreLab (ICIC,
2221 <http://imagecorelabcn.com/>), will be established with the aim of facilitating the central
2222 reading by clinicians and integrating medical imaging at the baseline control and
2223 each clinical visit. For details, please refer to *2.10 Assessments of imaging outcome*
2224 in the *2. Supplementary Methods*.

2225

2226

2227 **11. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS**

2228 **11.1 Regulatory and ethical compliance**

2229 The design, implementation and reporting of this trial will follow the principles of the
2230 Declaration of Helsinki (World Medical Association: Declaration of Helsinki, Ethical
2231 Principles for Medical Research Involving Human Subjects - Version 2008).

2232

2233 **11.2 Recruitment and informed consent form**

2234 Eligible patients who voluntarily agree to participate in the trial will be required to sign
2235 a written informed consent form (ICF). The ICF will be signed by the patients or
2236 his/her legal representative prior to randomization. They will be informed
2237 shortly by the investigators when the treatment is assigned after central
2238 randomization.

2239

2240 **11.3 Responsibilities of the investigator**

2241 Site investigators will review the eligibility of each candidate patient. If the patient is
2242 qualified and interested in this trial, he/she will be given written ICF to participate.
2243 Site investigators are responsible for explaining the research background,
2244 intervention, protocol, benefits, and risks of participating in the trial. A signed ICF
2245 copy will be kept by the patient as part of the study files. The patient is fully entitled
2246 to quit at any circumstance.

2247

2248 **11.4 Public disclosure and publication policy**

2249 As the sponsor of the study, Xuanwu Hospital aims to publicize the primary and
2250 secondary outcome results in a high-impact scientific journal. Database of this trial
2251 will be locked within 3 months when the last enrolled patient finished the scheduled
2252 3-year follow-up and all the data of the enrolled patients is completed. A manuscript
2253 will be submitted for potential publication in a scientific journal within 3 months after
2254 database lock. The manuscript will be shared with the financial sponsor(s) 3 months
2255 before submission, but the financial sponsor(s) have no influence on its contents.
2256 Anonymous data can be provided by principal investigators upon reasonable request.

2257

2258

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- 2368
- 2369

2370 **13. APPENDIX**

2371

2372 **13.1 Barthel Index (BI)**

2373 The Barthel scale is an ordinal scale used to measure performance in activities of
 2374 daily living (ADL). Each performance item is rated on this scale with a given number
 2375 of points assigned to each level or ranking. It uses ten variables describing ADL and
 2376 mobility. A higher number is associated with a greater likelihood of being able to live
 2377 at home with a degree of independence following discharge from hospital.

2378

Category	Scale definition
Feeding	0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent
Bathing	0 = dependent 5 = independent (or in shower)
Grooming	0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)
Dressing	0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)
Bowels	0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent
Bladder	0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent
Toilet use	0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)

Transfers (bed to chair and back)	0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent
Mobility (on level surfaces)	0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards
Stairs	0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent

2379

2380

2381

2382 **13.2 Modified Rankin Scale (mRS)**

2383

2384 The modified Rankin Scale is a commonly used scale for measuring the degree of
2385 disability or dependence in the daily activities of people who have suffered a stroke
2386 or other causes of neurological disability. The addition of grade 6 indicates dead.

2387

Grade	Disability	Descriptions
0	No symptoms	No symptoms
1	No significant disability	Able to carry out all usual activities, despite some symptoms.
2	Slight disability	Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability	Requires some help, but able to walk unassisted.
4	Moderately severe disability	Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability	Requires constant nursing care and attention, bedridden, incontinent.
6	Dead	Dead

2388

2389

2390 **13.3 NIH Stroke Scale**

2391

2392 The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool
 2393 used by healthcare providers to objectively quantify the impairment caused by a
 2394 stroke. The NIHSS is composed of 11 items, each of which scores a specific ability
 2395 between a 0 and 4. For each item, a score of 0 typically indicates normal function in
 2396 that specific ability, while a higher score is indicative of some level of impairment.
 2397 The individual scores from each item are summed in order to calculate a patient's
 2398 total NIHSS score. The maximum possible score is 42, with the minimum score
 2399 being a 0.

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Instructions	Scale definition
<p>1a. Level of consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.</p>	<p>0 = Alert; keenly responsive.</p> <p>1 = Not alert; but arousable by minor stimulation to obey, answer, or respond.</p> <p>2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).</p> <p>3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.</p>
<p>1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded</p>	<p>0 = Answers both correctly.</p> <p>1 = Answers one correctly.</p> <p>2 = Answers both incorrectly.</p>

<p>and that the examiner not "help" the patient with verbal or non-verbal cues.</p>	
<p>1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.</p>	<p>0 = Performs both tasks correctly.</p> <p>1 = Performs one task correctly.</p> <p>2 = Performs neither task correctly.</p>
<p>2. Best gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye</p>	<p>0 = Normal.</p> <p>1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.</p> <p>2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.</p>

<p>contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.</p>	
<p>3. Visual fields: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.</p>	<p>0 = No visual loss.</p> <p>1 = Partial hemianopia.</p> <p>2 = Complete hemianopia.</p> <p>3 = Bilateral hemianopia (blind including cortical blindness).</p>
<p>4. Facial palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.</p>	<p>0 = Normal symmetrical movements.</p> <p>1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling).</p> <p>2 = Partial paralysis (total or near-total paralysis of lower face).</p> <p>3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).</p>
<p>5. Arm motor: The limb is placed in</p>	<p>0 = No drift; limb holds 90 (or 45) degrees</p>

<p>the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.</p>	<p>for full 10 seconds.</p> <p>1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.</p> <p>2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.</p> <p>3 = No effort against gravity; limb falls.</p> <p>4 = No movement. UN = Amputation or joint fusion, explain: _____</p> <p>5a. Left Arm</p> <p>5b. Right Arm</p>
<p>6. Leg motor: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.</p>	<p>0 = No drift; leg holds 30-degree position for full 5 seconds.</p> <p>1 = Drift; leg falls by the end of the 5-second period but does not hit bed.</p> <p>2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity.</p> <p>3 = No effort against gravity; leg falls to bed immediately.</p> <p>4 = No movement. UN = Amputation or joint fusion, explain: _____</p> <p>6a. Left Leg</p> <p>6b. Right Leg</p>
<p>7. Limb ataxia: This item is aimed at finding evidence of a unilateral</p>	<p>0 = Absent.</p>

<p>cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.</p>	<p>1 = Present in one limb.</p> <p>2 = Present in two limbs.</p> <p>UN = Amputation or joint fusion, explain: _____</p>
<p>8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.</p>	<p>0 = Normal; no sensory loss.</p> <p>1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched.</p> <p>2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.</p>

<p>9. Best language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.</p>	<p>0 = No aphasia; normal.</p> <p>1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response.</p> <p>2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.</p> <p>3 = Mute, global aphasia; no usable speech or auditory comprehension.</p>
<p>10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.</p>	<p>0 = Normal.</p> <p>1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty.</p> <p>2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.</p> <p>UN = Intubated or other physical barrier, explain: _____ _____</p>

<p>11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.</p>	<p>0 = No abnormality.</p> <p>1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.</p> <p>2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.</p>
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2407 **13.4 Mori Classification**

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2409 The Mori classification, formulated on the basis of DSA, delineates the length and
2410 geometry of intracranial stenosis as follows:

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Type	Descriptions
A	short (5 mm or less in length) concentric or moderately eccentric lesions less than totally occlusive
B	tubular (5 to 10 mm in length) extremely eccentric or totally occluded lesions, less than 3 months old
C	diffuse lesions (more than 10 mm in length), extremely angulated (>90°) lesions with excessive tortuosity of the proximal segment or totally occluded lesions, 3 months old or older

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2414 **13.5 TICI perfusion categories**

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2416 The thrombolysis in cerebral infarction (TICI) grading system was described as a tool
 2417 for determining the response of thrombolytic therapy for ischemic stroke. In
 2418 interventional neuroradiology, it is commonly used for patients post endovascular
 2419 revascularization. Like most therapy response grading systems, it predicts prognosis.

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Grade	Descriptions	
0	No Perfusion. No antegrade flow beyond the point of occlusion.	
1	Penetration With Minimal Perfusion. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.	
2	Partial Perfusion. The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, e.g., the opposite cerebral artery or the arterial bed proximal to the obstruction.	
	2a	Only partial filling (<2/3) of the entire vascular territory is visualized.
	2b	Complete filling of all of the expected vascular territory is visualized, but the filling is slower than normal.
3	Complete Perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.	

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2422 **13.6 ASITN/SIR collateral flow grading system**

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2424 ASITN/SIR refers to American Society of Interventional and Therapeutic
2425 Neuroradiology/Society of Interventional Radiology (ASITN/SIR). The grading
2426 system scale is determined on DSA, classifying the cerebral collateral status ranging
2427 from grade 0 to 4. Grades 0-1, 2 and 3-4 are usually regarded as poor, moderate
2428 and good collateral flow.

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Grade	Descriptions
0	No collaterals visible to the ischemic site
1	Slow collaterals to the periphery of the ischemic site with persistence of some of the defect
2	Rapid collaterals to the periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory
3	Collaterals 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

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CASSISS Study Protocol: Summary of Changes (Version 1.0 ⇒ Version 3.0)

CASSISS Study: China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis

Prepared: May 1st, 2015

#	Item	Page	Description of change(s)		Reasons for change
			Before change (Version 1.0, date prepared: March 4 th , 2013)	After change (Version 3.0, date prepared: May 1 st , 2015)	
1	Secondary outcome	<p>2. Summary (Page 9-10)</p> <p>3.5.2 Secondary objectives (Page 13)</p> <p>6.2 Secondary endpoints (Page 21)</p>	<p>Secondary outcome:</p> <ul style="list-style-type: none"> • Disabling stroke or death beyond 30 days through 3 years in both arms; • Complication rates associated with stenting procedures; • Restenosis (>50%) related to stenting within a follow-up of 3 years; • Any stroke, severe TIA, or cardiovascular events within a follow-up of 3 years; • National Institutes of Health Stroke Scale (NIHSS), mRS, and Barthel index assessment within a follow-up of 3 years; • The compliance rate of the patients with regular medical therapy within a follow-up of 3 	<p>Secondary outcome:</p> <ul style="list-style-type: none"> • Disabling stroke or death after enrollment through 3 years in both arms; • 2-year rate of the same-territory stroke; • 3-year rate of the same-territory stroke; • Any stroke, TIA, or cardiovascular events within a follow-up of 3 years. • Death rate in both arms within a follow-up of 3 years. 	Due to content revisions

			<p>years;</p> <ul style="list-style-type: none"> Death rate in both arms within a follow-up of 3 years. 		
2	Medical therapy	<p>4. Study design (Page 14)</p> <p>6.7.1 Medical therapy (Page 24)</p> <p>6.8.1 PTAS procedure (Page 26)</p>	<p>Medical therapy includes both aspirin 100 mg plus clopidogrel 75 mg per day for 90 days (aspirin 100 mg alone per day thereafter) and management of risk factors.</p>	<p>Medical therapy includes both aspirin 100 mg plus clopidogrel 75 mg per day for 90 days (aspirin 100 mg or clopidogrel 75mg alone per day thereafter) and management of risk factors.</p>	Due to content revisions
3	Severe TIA	6.3 Definitions of endpoints (Page 22)	<ul style="list-style-type: none"> Severe TIA refers to rapidly developed clinical signs of focal or global disturbance of cerebral function lasting longer than 10 minutes but fewer than 24 hours, without apparent nonvascular cause. 	Deleted	Due to content revisions

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