Multimodal Neuronavigation Guiding Precision Bypass in Adult Ischemic Patients With Moyamoya Disease (PBM)

—— A Prospective, Single-center, Randomized Controlled Trial ——

Study Protocol

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April 21, 2018

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1. Abbreviations

ACA	Anterior Cerebral Artery
ACE	Angiotensin Converting Enzyme
ADA	American Diabetes Association
AE	Adverse Event
ALT	Alanine transaminase
ASL	Arterial Spin Labeling
AST	Aspartate aminotransferase
ARB	Angiotensin Receptor Blocker
BMI	Body Mass Index
BP	Blood Pressure
CBF	Cerebral blood flow
CEC	Clinical Events Adjudication Committee
CFDA	China Food and Drug Administration
CI	Confidence Interval
CRF	Case Report Form
CT	Computer Tomography
CTP	Computed Tomography Perfusion
DICOM	Digital Imaging and Communications in Medicine
DSA	Digital Subtraction Angiography
DSMB	Data Safety Monitoring Board
EoT	End of Trial
FAS	Full Analysis Set
HDL	High Density Lipoprotein
ICG	Indocyanine Green
IDL	Intermediate Density Lipoproteins
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	Low Density Lipoprotein
MCA	Middle Cerebral Artery

MI	Myocardial Infarction
MMD	Moyamoya Disease
MoCA	Cognitive Functional Outcome by the Montreal Cognitive Assessment
MR	Magnetic Resonance
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STA	Superficial Temporal Artery
TIA	Transient Ischemic Attacks
UADE	Unanticipated Adverse Device Effect
VLDL	Very Low Density Lipoproteins

2. **Protocol Synopsis**

Title	Multimodal Neuronavigation Guiding Precision Bypass in Adult Ischemic Patients with Moyamoya Disease
Acronym	PBM
Objectives	To determine whether direct bypass surgery guided by multimodal neuronavigation is superior to empirical direct bypass procedure for preventing the primary endpoint (All strokes & death within 30 days post-surgery and ipsilateral hemorrhage afterwards) after cerebral revascularization surgery in ischemic MMD patients.
Study Design	This will be an investigator-initiated and single center trial in which patients with ischemic symptoms (such as TIA, stroke) or asymptomatic MMD after symptom onset prior to enrollment that is caused by stenosis or occlusion in the terminal portion of the internal carotid artery and/or the initial portion of the anterior or middle cerebral arteries unilaterally or bilaterally and formation of abnormal collateral networks (moyamoya vessels) at the base of the brain will be randomized (1:1) to: Direct bypass surgery guided by multimodal neuronavigation. Combine local cerebral blood flow velocity and superficial perfusion assessed by Flow800 software that implements conventional ICG fluorescence angiography and deep perfusion assessed by multimodal MR (structure combined with perfusion sequence) to determine the recipient vessel. OR Empirical direct bypass surgery.
Primary endpoint	All strokes & death within 30 days post-surgery and ipsilateral hemorrhage afterwards
Secondary endpoint	• All kinds of adverse events related to surgery within 30 days • Infarctions on the contralateral side within 2 years of randomization • Transient ischemic attack on the surgically treated side within 2 years of randomization

	• The changes from baseline in CBF measured by ASL at 7days, 3 months, 6 months, 12 months or end of trial • The changes from baseline in modified Rankin Scale (mRS) at 7 days, 3 months, 6 months, 12 months or end of trial • The changes from baseline in National Institute of Health Stroke Scale (NIHSS) at 7 days, 3 months, 6 months, 12 months or end of trial • The changes from baseline in modified Barthel Scale at 7 days, 3 months, 6 months, 12 months or end of trial
Inclusion Criteria	• Independent in activity of daily living(The modified Rankin Scale 0-2) • At least one month since the most recent ischemic stroke • The neurological deficit must be stable for more than 6 weeks • Digital substraction angiography demonstrating progressive stenosis or occlusion in the terminal portion of the internal carotid artery and/or the initial portion of the anterior or middle cerebral arteries • Digital substraction angiography demonstrating formation of abnormal collateral networks(moyamoya vessels) at the base of the brain,mainly in the region of thalamus and basal ganglia • Digital substraction angiography demonstrating the vasculopathy appeared unilaterally or bilaterally • Competent to give informed consent • Accessible and reliable for follow-up
Key Exclusion Criteria	• Other diseases(such as internal carotid artery stenosis, internal carotid artery dissection, atrial fibrillation, or Intracranial atherosclerosis) probably causing ischemic strokes • Not independent in activity of daily living(The modified Rankin Scale 3-5) • Moyamoya syndrome concomitant with other hereditary or autoimmune diseases(Grave's

	Disease,Type I Diabetes Mellitus,Type I Neurofibromatosis et al) • Patient whose initial onset was marked by ischemia but subsequently suffered from intracranial hemorrhage • Emergent evacuation of intracerebral hematoma damaging superficial temporal artery or cortical artery • Emergent decompressive craniotomy causing automatically developed indirect revascularization • Good collateral networks formed by spontaneous anastomosis between extracranial and intracranial vessels before surgery • Life expectancy<1 years • Pregnancy • Unstable angina or myocardial infarction with recent 6 months • Blood coagulation dysfunction • Allergic to iodine contrast agent • Abnormal liver function(alanine transaminase(ALT) and/or aspartate aminotransferase(AST)>3 times of normal range) • Serum creatinine >3mg/dl • Poorly controlled hypertension(systolic BP>160 mmHg,diastolic BP>100 mmHg) • Poor glucose control(fasting blood glucose>16.7mmol/l) • Concurrent participation in any other interventional clinical trial • patients refused to participate in the study
Sample Size	Finally, 100 patients are randomized (1:1) to two groups, 50 of them will undergo direct bypass guided by multimodal neuronavigation, while others will undergo empirical direct bypass procedure.

Follow-up	The face-to-face interview will be performed by study neurologists at 7 days, at discharge, at 3 months, at 6 months and at 12 months (or by telephone) after the recruitment of patients.

3. Study Rationale

Epidemiology of MMD

Moyamoya disease (MMD) was originally considered to affect predominantly east Asian populations, has now been observed throughout the world in people of many ethnic backgrounds, including American and European heritage.[1-3] The distribution of age at onset has been suggested to have two peaks: children who are approximately 5 years of age and adults with a lower peak in their mid-40s.[1, 2, 4-7] Meanwhile, female patients are nearly twice as male patients.[1, 2, 4, 7, 8] As the most common pediatric cerebrovascular disease in Japan, MMD has a prevalence of 3 cases per 100,000 children.[4, 7, 9] While in Europe the incidence of MMD appears to be only 1/10th of that observed in Japan.[10] Results from a 2005 American review which involved 298 patients with MMD suggests a lower incidence of 0.086 per 100,000.[11] And the incidence rate ratios of specific ethnic origins compared with whites were 4.6 for Asian Americans, 2.2 for African Americans, and 0.5 for Hispanics.[11] Epidemiology studies in mainland China are rare. Miao and co-workers[12] collected data from 202 patients with moyamoya disease in Nanjing between 2000 and 2007 and found the incidence to be 0.43 per 100,000, with female-to-male ratios of 1:1.[13] Furthermore, familial occurrence of MMD has been variably reported: 1.5%[12] or 5.2% in China,[13] and 10%-15% in Japan.[3, 4]

Risk of Stroke or Hemorrhage for MMD

The greatest concern for MMD is the risk of subsequent stroke or hemorrhage even with surgical revascularization and regular medical therapy. A retrospective, single-center, cohort study showed most subsequent ischemic events appeared in the first 2 years after surgery. The Kaplan-Meier estimated stroke risk was 10.1% and 12.7% in the first 2 years and 5 years after surgery for all patients treated with surgical revascularization, approximated 10.1% incidence of mortality or TIA or stroke at 1 year after surgery in 802 patients with the MMD.[13] Incidence of rebleeding range from 12.5~20% of patients with onset hemorrhage symptom who underwent revascularization surgery, while with the conservation treatment the rebleeding estimated occurrence of 6.8–65%.[14-18]

Medical Management for MMD

Medical management has been used in patients with MMD, especially when the risk of surgery has been considered to be high or the patient's condition is relatively mild, but there are few data showing either its short-term or long-term efficacy. Antiplatelet agents such as aspirin have been used to prevent emboli from microthrombi formed at sites of arterial stenosis, which may cause ischemic symptoms in patients with MMD, although these agents are not used universally, are used routinely in patients in many

operative series.[8] Anticoagulants such as warfarin are rarely used, although there has been some experience with the use of low-molecular- weight heparin.[19, 20] Calcium-channel blockers can be used to ameliorate intractable headaches or migraines, which are commonly seen in patients with MMD. At the same time, these agents may be also effective in reducing both the frequency and the severity of refractory TIA. However, care must be taken when using them in this patient population due to the role of causing hypotension. Although a large survey from Japan showed no significant differences in outcome between medically and surgically treated patients with MMD.[12] Some recent studies suggest patients with surgical treatment have fewer ischemic events and better life qualities than medical treatment.[21]

Surgical treatment for MMD

Revascularization surgery has played an important role for treatment of MMD. Several general methods of revascularization had been used: direct, indirect and combined techniques. Two large studies with long term follow-up showed a good safety profile for surgical treatment. During the postoperative 30 days the risk of stroke is highest (approximately 4% per hemisphere); and after the first month, the risk decreases fairly. It is reported that patients have a 96% probability of remaining stroke-free over the subsequent 5 years.[8, 22] Patients with MMD have a higher risk of perioperative ischemic events. The complications associated with the treatment include stroke, infection, and intracranial hemorrhage.

Currently, there are no reports on the MMD research that refer to the criteria of receptor vessel selection in bypass surgery for MMD. Surgeons usually performed superficial temporal artery to MCA (STA–MCA) anastomosis.[23] Sometimes when patients have severe ischemia in ACA area the STA can also be anastomosed to the branch of the ACA.[24, 25] So precisely choosing receptor vessel remains uncertain. As the imaging advanced, ASL can be used as a perfusion method to detect the ischemia area and intraoperative ICG angiography using Flow800 software can be used to reflect the lower flow velocity and superficial perfusion. Guided by this two imaging data, we try to precisely find the receptor vessel.

4. Primary Aim and Hypothesis

Primary Aim

To determine whether direct bypass surgery guided by multimodal neuronavigation is superior to empirical direct bypass procedure alone for preventing the primary endpoint (All strokes & death within 30 days post-surgery and ipsilateral hemorrhage afterwards) after cerebral revascularization surgery in ischemic MMD patients.

*patients with TIA, stroke or other ischemic symptoms prior to enrollment that is attributed to progressive stenosis or occlusion in the terminal portion of the internal carotid artery and/or the initial portion of the anterior or middle cerebral arteries unilaterally or bilaterally and formation of abnormal collateral networks (moyamoya vessels) at the base of the brain.

Primary Hypothesis

As compared with empirical direct bypass procedure alone, direct bypass surgery guided by multimodal neuronavigation will decrease the risk of the primary endpoint over 12 months in patients with MMD.

5. Study Plan and Procedure

Study Design and Flow Chart

This will be an investigator-initiated and Phase III single center trial in which patients with TIA, stroke or other ischemic symptoms prior to enrollment that is attributed to progressive stenosis or occlusion in the terminal portion of the internal carotid artery and/or the initial portion of the anterior or middle cerebral arteries unilaterally or bilaterally and formation of abnormal collateral networks (moyamoya vessels) at the base of the brain will be randomized (1:1) to:

Direct bypass surgery guided by multimodal neuronavigation. Combine local cerebral blood flow velocity and superficial perfusion assessed by Flow800 software that implements conventional ICG fluorescence angiography and deep perfusion assessed by multimodal MR (structure combined with perfusion sequence) to determine the recipient vessel.

OR

Empirical direct bypass surgery.

The evidence-based program of risk factor management will be administered to all patients by the study neurosurgeon at each site at regularly scheduled times throughout the study.

6. Study Endpoints

6.1. Primary Endpoint

All strokes & death within 30 days post-surgery and ipsilateral hemorrhage afterwards

6.2. Clinical Secondary Endpoint

- All kinds of adverse events related to surgery within 30 days
- Infarctions on the contralateral side within 1 year of randomization
- Transient ischemic attack on the surgically treated side within 1 year of randomization

- The changes from baseline in CBF measured by ASL at 7days, 3 months, 6 months, 12 months or end of trial
- The changes from baseline in modified Rankin Scale (mRS) at 7 days, 3 months, 6 months, 12 months or end of trial
- The changes from baseline in National Institute of Health Stroke Scale (NIHSS) at 7 days, 3 months, 6 months, 12 months end of trial
- The changes from baseline in modified Barthel Scale at 7 days, 3 months, 6 months, 12 months or end of trial

7. Patient Selection Criteria

7.1. Inclusion criteria

- Independent in activity of daily living(The modified Rankin Scale 0-2)
- At least one month since the most recent ischemic stroke
- The neurological deficit must be stable for more than 6 weeks
- Digital substraction angiography demonstrating progressive stenosis or occlusion in the terminal portion of the internal carotid artery and/or the initial portion of the anterior or middle cerebral arteries
- Digital substraction angiography demonstrating formation of abnormal collateral networks (moyamoya vessels) at the base of the brain, mainly in the region of thalamus and basal ganglia
- Digital substraction angiography demonstrating the vasculopathy appeared unilaterally or bilaterally
- Competent to give informed consent
- Accessible and reliable for follow-up

7.2. Exclusion Criteria

- Other diseases(such as internal carotid artery stenosis, internal carotid artery dissection, atrial fibrillation, or Intracranial atherosclerosis) probably causing ischemic strokes
- Not independent in activity of daily living(The modified Rankin Scale 3-5)
- Moyamoya syndrome concomitant with other hereditary or autoimmune diseases (Grave's Disease,Type I Diabetes Mellitus,Type I Neurofibromatosis et al)
- Patient whose initial onset was marked by ischemia but subsequently suffered from intracranial hemorrhage
- Emergent evacuation of intracerebral hematoma damaging superficial temporal artery or cortical artery
- Emergent decompressive craniotomy causing automatically developed indirect revascularization
- Good collateral networks formed by spontaneous anastomosis between

extracranial and intracranial vessels before surgery

- Life expectancy<1 years
- Pregnancy
- Unstable angina or myocardial infarction with recent 6 months
- Blood coagulation dysfunction
- Allergic to iodine contrast agent
- Abnormal liver function(alanine transaminase (ALT) and/or aspartate aminotransferase (AST)>3 times of normal range)
- Serum creatinine >3mg/dl
- Poorly controlled hypertension (systolic BP>160 mmHg,diastolic BP>100 mmHg)
- Poor glucose control (fasting blood glucose>16.7mmol/l)
- Concurrent participation in any other interventional clinical trial
- patients refused to participate in the study

8. Informed Consent

The principles of Informed Consent, according to FDA Regulations and ICH guidelines on GCP, will be followed. Investigator will submit a copy of the proposed consent form, together with the study protocol, to the central Institutional Review Board (IRB) at Peking University International Hospital for approval. Each eligible patient who wishes to participate in this study will be invited to give written informed consent. Before the consent is signed, a trained researcher will explain study purpose, description, duration, potential risks and anticipated benefits, cost and compensation, voluntary nature of participation, appropriate alternatives, treatment for study-related injury, whom to contact with questions or concerns or study-related injuries, maintenance of confidentiality of record, and funding source. Patients will be encouraged to consent for the blood drawing for biomarker testing only if they would be prepared to enroll in the trial.

9. Enrollment of Patients

All of Patients who meet the clinical criteria will undergo MRI, CTP and DSA. Patients with progressive stenosis or occlusion in the terminal portion of the internal carotid artery and/or the initial portion of the anterior or middle cerebral arteries unilaterally or bilaterally and formation of abnormal collateral networks (moyamoya vessels) at the base of the brain according to DSA, hypoperfusion based on perfusion CT or DSA and no significant new infarction lesions on MRI will be asked to participate and sign consent. Once this is completed, the patient will be enrolled and, if randomized to multimodal neuronavigation guiding precise bypass group, will undergo multimodal neuronavigation guiding precise bypass surgery after enrollment.

10. Randomization of Patients

The central randomized method based on our own system. Patient who has signed the informed consent form and met all inclusion criteria without any exclusion item could be enrolled. Once the patient enrolled in the study, the system will automatically assign the study patient a random number with the exact group that he/she should be treated. Then the investigator should record this number and group in the original case history and the coming treatment record of the study patient. According to the protocol, this patient should be treated into the randomized group or the control group.

The investigator's team should archive the randomized list and the related documents (randomized application form) together in the trial folder, which clinical trial department of the site has to store.

11. Image Data Evaluation

Considering the quality of the angiographic images in the trial, we will select participating sites which are available to have access to state-of-the-art cerebral angiography facilities. The investigators in each site will be trained and certificated for image acquisition and measurement before the startup phase of the trial.

The angiographic imaging showed internal carotid artery stenosis/occlusion site, moyamoya vessels and vascular compensatory level. MRI should contain structure sequence and ASL sequence.

When a patient is enrolled in the trial, core lab will obtain CD copies of angiographic images, CT perfusion and MRI for central review. Images of the cerebral artery，CT perfusion and MRI post revascularization surgery also must be sent to core lab for central review.

12. Multimodal Neuronavigation Procedure

Pre-procedure: All patients randomly assigned to both arms will be suspend aspirin 7 days before the revascularization procedure and restart taking aspirin on the first day postoperatively.
Intra-procedure: The surgical procedure will be done under the general anesthesia. ICG fluorescence angiography using Flow800 software and electromagnetic neuronavigation system is required during the procedure of revascularization. An

initial ICG fluorescence angiography will be performed when the dural membrane is unfold to expose the blood vessels on the surface of the brain. According to the appearance order of vessels to assess the velocity of cerebral flow. Neuronavigation system is used to judge the cerebral hypoperfusion area under different recipient vessels. The vessel was chose as the receptor with lower flow velocity and lower cerebral perfusion area to perform anastomosis.

Papaverine is used to prevent the occurrence of vasospasm. During surgery, the heparinized water was used to flush the donator's and the receptor's lumen for minimization of thrombosis or thromboembolism risk. An anastomotic end-to-side continuous (or intermittent) suture was performed using a 10-0 nonabsorbable vascular suture thread.

Post-procedure: Aspirin 100mg per day must be used for the entire duration of follow-up. Clopidogrel is not necessary after the surgery unless cardiologist recommends taking clopidogrel for a cardiac indication.

13. Antithrombotic therapy

All participants will take aspirin 100 mg per day for entire follow-up after the revascularization surgery. Suspend aspirin 7 days before surgery, if necessary (Previous vascular stent implantation history), replace the treatment with low molecular weight heparin. If patients have been prescribed long-term use of clopidogrel for indications of coronary disease or peripheral vascular disease, taking clopidogrel at the same time..

14. Management of Risk Factor

14.1. Primary Risk Factors

Blood Pressure Control

Measurement and treatment of blood pressure (BP) in this study will be based on JNC 7 guidelines. The trained study coordinators at each participating site perform blood pressure measurement using standardized blood pressure monitors. Blood pressure will be measured at randomization, at discharge, at 3 months, at 6 months, and at the end of trial. Some patients would be required to come back to clinic for checking blood pressure and to modify regimen of blood pressure management. Given a likelihood of impaired cerebral perfusion resulting subsequent stroke,33 blood pressure of 130-140/90-95 mmHg will be maintained regardless of patients have diabetes or not. Patients will be considered "in target" when the blood pressure at one visit is under ranges of 130-140/90-95 mmHg.

Antihypertensive drug (Angiotensin-converting enzyme [ACE] inhibitor, Angiotensin Receptor Blocker [ARB], beta-blocker, calcium channel antagonist, diuretic, vasodilator, etc.) will be not free of charge to study patients. Drugs can be chased from each participating site for use by study patients.

As part of routine care, serum creatinine will be checked at baseline, at 3 months, at 6 months, and at the end of trial. It will be anticipated that a repeating test of serum creatinine during a period of follow-up might be required one month after changing dose of an ACE inhibitor or for assessing whether renal function is impaired or not. Additionally, all patients will have a potassium level checked at randomization, one month after changing the dose of a diuretic or ACE inhibitor, at 3 months, and 6 months after study entry.

14.2. Secondary Risk Factors

Non-HDL Cholesterol

Non-HDL cholesterol <100 mg/dL is considered an important secondary target. Non-HDL cholesterol contains LDL, very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL). Once the dose of statin has been not increased to lower LDL, if non-HDL cholesterol >= 100 mg/dL and triglycerides >=200mg/dL, fenofibrate (Tricor) 145 per day will be recommended to patients.

Treatment for Diabetes

HgA1c < 7.0% will be the target of diabetes management according to recommendations of the American Diabetes Association (ADA). HgA1c testing should be performed at baseline, at 3 months, and at 6 months to ensure glycemic goals to be met. Other items about management of diabetes are based on Recommendations from ADA Position Statement for Standard of Medical Care in Diabetes (ADA, 2006). Achieving good diabetic control might need a cooperation of a multidiscipline team including patients, study neurologists, primary physicians, and even endocrinologists.

Smoking Cessation

Study investigators at each site will assess current smoking status and cigarette quantity per day at every study visit. Every study patient will be educated or encouraged to quit smoking at study entry and during follow-up, as appropriate.

Management of Body Weight

Weight will be assessed at each follow-up visit and body mass index (BMI) calculated by dividing measured weight in kilograms by the square of measured height in meters. Targeted goals of BMI management depend on the initial BMI: the target BMI is < 25 kg/m^2 if the initial BMI is 25-27 kg/m^2; a 10% weight reduction will be targeted if the initial BMI >27 kg/m^2. Details for weight management are based on 2013 AHA/ACC/TOS Guidelines for Treatment of Overweight and Obesity in Adults.

Medications
ASA counts will be done for assessment of patient compliance at every study visit.

Atorvastatin will be given to study patients with LDL > 70 mg/dL. If other lipid-lowering drug is taken, patients will be encouraged to switch to atorvastatin. But, it is not mandatory.

Study patients not achieving the target of blood pressure will be prescribed antihypertensive drugs. Patients can choose but not limited to the following drugs for antihypertension:

- ✧ A diuretic (chlorthalidone 25 mg)
- ✧ an ACE inhibitor (lisinopril 10 and 40 mg)
- ✧ an angiotensin receptor blocker (candesartan (Atacand) 16 and 32 mg)
- ✧ a beta-blocker (atenolol 50 and 100 mg)
- ✧ a vasodilator (hydralazine 50 mg)
- ✧ a central alpha agonist (clonidine 0.1 mg)
- ✧ a long-acting calcium channel antagonist (felodipine 5 and 10 mg)

Exercise
Physical activity status will be assessed at each study visit by study trained investigators or coordinators according to Guide to the Assessment of Physical Activity of the American Heart Association (Clinical and Research Applications). Physical activity will be strongly encouraged to all enrolled patients. Moderate intensity activities will be recommended at least 3 times per week for 30 minutes per session if patients have ability to do it.

15. Leading Phase of Trial for Site Selection

Candidate sites for trial will be initially identified based on hospital grades, the intervention experience, and the volume of revascularization surgery cases. It will take three months before the trial kickoff for the steering committee to assess site research capability and commitment to the study. The center meeting the following criteria will be enrolled into the trial: ① at least 5 cased will be recruited within the leading phase; ② the rate of perioperative complications should be not more than 15% (stroke or death).

16. Schedule of Follow-up and Post-study Follow-up Period

All patients will be followed up until the primary endpoint or the end of the trial. Complete endpoint information will be obtained with the best effort irrespective of

patient study status, unless patients withdraw consent to participate the trial. Patients will continue to be followed up beyond date of consent withdrawal if they stop the trial and receive other treatment such as medical therapy but agree to provide the prognostic information. The face-to-face interview will be performed by study neurologists at discharge, at 3 months, at 6 months and at 12 months (or by telephone) after the recruitment of patients. If they are more convenient to have access to the study site near to their living areas, patients will be allowed to go to the site for their follow-up.

Visits	**Windows**	**Definition**
Randomization	0 day	Study Day 0 day
At discharge	0 day	Based on the number of hospitalization days
At 3 month	7 days	Day 83-97
At 6 months	14 days	Day 166-194
At 12 months	30 days	Day 330-390

Note: 1 month= 30 days

The following procedures will be done at 3 months, at 6 months after enrollment:

- ✧ A neurological evaluation will be performed (Modified Rankin Scale, National Institute of Health Stroke Scale, modified Barthel Scale);
- ✧ A physical examination will be performed, including vital signs (blood pressure, heart rate);
- ✧ Information will be collected on medications, risk factors, and events of interest since the last visit;
- ✧ Computed Tomography Perfusion (CTP), Magnetic Resonance (MR) and Digital substraction angiography (DSA) will be performed;

The following evaluations will be done at the end of trial:

- ✧ Lab tests for diabetic control and hyperlipidemia management will be performed;
- ✧ A neurological evaluation will be performed (Modified Rankin Scale, National Institute of Health Stroke Scale, modified Barthel Scale);
- ✧ A cognitive function evaluation will be performed (MoCA);
- ✧ Computed Tomography Perfusion (CTP) and Magnetic Resonance (MR) will be done if a patient does not experience a primary endpoint before the end of trial. Images will be transferred to the core imaging evaluation lab.
- ✧ Information will be collected on medications, risk factors, and events of interest since the last visit;

Post study Follow-up Period

All patients will be followed every 12 months by study personnel after the EoT. Any treatment beyond the EoT is at the discretion of the treating physicians. The primary or secondary endpoints will be collected every 12 months since the EoT by telephone interview.

17. Management of Ischemic Events with Temporary Signs during Follow-up

If a patient in either treatment arm develops a potential clinical neurological event (TIA, ischemic stroke), an adjudication packet will be produced by the site within 72 hours. Vascular imaging including angiography will be at the discretion of study neurosurgeon. If primary endpoint occurs, MRI will be performed. Since the most effective therapy is unknown for MMD patients with frequently TIA or recently ischemic stroke, it will be not recommended for patients to receive multimodal neuronavigation bypass or empirical bypass. However, the patient's risk factors should be in target goals.

If patients in the both arms experience TIA or ischemic stroke postoperatively associated with MRI proven infarctions, continued medical therapy alone for them will be recommended by study investigators consisting of neurosurgeons. Decompressive craniectomy will be not recommended to patients without risk of cerebral hernia who have an ischemic stroke.

Additionally, if patients have reached a primary endpoint, that is, stroke in the territory of surgery side, any treatment after occurrence of stroke will be not monitored by investigators and at the discretion of treating physicians.

18. Evaluation of End Points and Adverse Events

- **Adverse Event (AE):** An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product or device, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.
- **Serious Adverse Event (SAE):** A serious adverse event is an AE occurring during any study phase that fulfils one or more of the following criteria:

i. Results in death,
ii. Is life-threatening,
iii. Requires inpatient hospitalization or prolongation of existing hospitalization,
iv. Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
v. Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

- **Unanticipated Adverse Device Effect (UADE):** Any serious adverse effect on health

or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of subjects.
The following events have been identified as possible complications of revascularization surgery and are considered anticipated:

Vasospasm	Surgical Intervention	Arrhythmia
Vessel dissection	Neurological symptoms	Cardiac ischemia
Vessel occlusion	Pain	Coagulopathy
Vessel perforation	Pseudoaneurysm	Death
Vessel rupture	Renal insufficiency / failure	Emboli (air, tissue, thrombus or foreign body)
Vessel thrombosis	Respiratory Distress / failure	Hematoma, pain, and/or infection at access site
Stroke	Seizure	Hemorrhage
Transient ischemic attack	Infection	Hypertension
Syncope	Drug reaction to antiplatelet medication	Hypotension

19. Core Lab

The core lab for imaging assessment is located at Peking University International Hospital. The Digital Imaging and Communications in Medicine (DICOM) imaging data will be collected, transported, and stored according to standardized protocol developed by lab committee. Imaging for diagnosis of MMD, hypoperfusion in the territory of culprit artery, event adjudication will be reviewed by specialists with experience in MR and angiography who are blinded to demographic and clinical characteristics and treatment assignment.

20. Quality Assurance

Periodic monitoring and auditing will be performed at each site to ensure that data generated during the study reflect what is specified in the protocol, and data consistence by comparing data in the case report form (CRF) and data collected in source documents for (CRF vs. source documents). If patients who have events go to non-study sites for treatment, source documents will be photocopied for review. It should be guaranteed that the study investigators and relevant study personnel are available during the monitoring visits and possible audits.

21. Statistical Consideration

This section is an overview of the statistical considerations. Complete details can be found in the Statistical Analysis Plan (SAP). It provides the general specifications for the analysis of the data to be collected and presented in the Clinical Study Report. A final SAP will be issued prior to database lock and before code breaking. The SAP will define all "pre-specified, planned analyses."

21.1. Sample size estimates

Because this trial is a prospective, exploratory, randomized controlled trial, there is no previous data for multimodal neuronavigation guiding precise bypass procedure, the sample size for this trial can't be calculated from the formula. Finally, 100 patients are randomized (1:1) to two groups, 50 of them will undergo direct bypass guided by multimodal neuronavigation, while others will undergo empirical direct bypass procedure.

21.2. Description of analysis sets

All patients who have been randomized to study treatment will be included irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed based on the initial treatment assignment irrespective of whether the event occurred before or following discontinuation of study medication. Patients who withdraw consent to participate in the study will be included up to the date of their study termination except for vital status known through public records (for use in the analysis of all cause death). All efficacy variables will be analyzed using the full analysis set (FAS).

21.3. Statistical Analyses

All analyses will be based on the intent-to-treat principle using the FAS, including only events adjudicated by the Clinical Events Adjudication Committee (CEC). The primary hypothesis will be tested using a Cox proportional hazards model with a factor for the treatment group. The time to the first event was used in the model when there were multiple events of the same type. P values and Confidence Intervals (CI) for the Hazard Ratio will be obtained according to the Wald statistic. The following statistics, in addition to HR with CI will be also presented in the summary tables of these analyses: the number of patients with event and Kaplan-Meier estimates of the event rate per treatment group calculated at EoT. Kaplan-Meier estimates of the cumulative proportion of patients with primary endpoint events will be calculated and plotted.

The potential impact of loss to follow-up will be evaluated by the sensitivity analysis.

A Cox proportional hazards model will be used to assess differences between study groups in the rate of primary endpoint under the following three scenarios: (1) all patients will be thought to experience primary endpoint event when the final disposition for the event adjudication is not determined. (2) only patients in the empirical bypass arm will be thought to experience primary endpoint event when the final disposition for the event adjudication is not determined. (3) only patients in the multimodal neuronavigation guiding bypass arm will be thought to experience primary endpoint event when the final disposition for the event adjudication is not determined. These results under the three scenarios will be compared with the result under the scenario in which all patients will be not thought to have primary endpoint event when the final disposition for the event adjudication is not determined. However, the primary analysis result will be reported in patients who are censored not to have the event occurrence when the final disposition for the event adjudication is not determined.

The analysis of and the secondary efficacy variable for the test of multimodal neuronavigation guiding bypass against empirical bypass will comprise the confirmatory analysis. No multiplicity adjustment will be made in all analysis including a confirmatory testing (subgroup analysis).

21.4. **Clinical Site Effect**

All revascularization surgeries will be performed by the same experienced neurosurgeon.

21.5. **Subgroup analysis**

All analysis of effect of revascularization surgery on outcomes by pre-specified subgroups will be conducted:

- ✧ Age
- ✧ Gender, men vs. women
- ✧ hypertension, yes vs. no
- ✧ diabetes, yes vs. no
- ✧ Smoking, yes vs. no
- ✧ Post infarction, yes vs. no
- ✧ Suzuki grade I, II, III, IV, V, VI
- ✧ Operation time
- ✧ BMI, <25, 25-30, ≥ 30 Kg/m^2
- ✧ Hypoperfusion (CTP, ASL),

21.6. **Pre-specified exploratory analyses**

- ✧ Blood flow (ASL)
- ✧ Vascular morphology of internal carotid artery and moyamoya vessels

21.7. **Interim analyses**

One interim analysis will be planned and conducted by the Data Monitoring Committee following the accrual and confirmation by adjudication of 50% of planned primary events. The stopping rule of Lan-DeMets approach to O'Brien-Fleming[35,36] will be adopted for stopping for efficacy or futility. The efficacy stopping boundary at the interim analysis is a 2-sided p-value <0.0015 for the primary endpoint (one-year stroke or death). The final last level of significance with one interim analysis will therefore be 0.0489, with the family wise error rate controlled at 5.00%. The trial would be halted due to futility if nominal critical point (Standardized Z scale) for the primary endpoint crosses the internal boundary for futility (±0.595). It will be determined by the executive committee that the trial will be continued or stopped due to the overwhelming efficacy or futility after recommendation of Data Safety Monitoring Board.

21.8. **Censoring**

Patients who have not had the event(s) in question will be censored at the earliest of EoT visit and the last study contact when all components of the endpoint in question were assessed. Lost patients in whom we cannot accurately determine if the primary endpoint occurred will be censored at the last contact date at which the patient was known to be free from a primary endpoint.

If the study is stopped early at the interim analysis, the mentioned-above censoring rule will apply. When the trial is determined to be stopped, all patients who have not completed the treatment period will be required for a EoT visit as soon as possible.

22. Data Safety Monitoring Committee

A Data Safety Monitoring Board (DSMB) is composed of Academic Members, including an independent statistician, who are not otherwise participating in the trial. A DSMB charter including membership role and responsibilities will be approved by both the DSMB and the Executive Committee before the start of the trial. DSMB will meet approximately every three months to review the progress of this study (e.g enrollment, site performance, meeting risk factor targets) as well as data on the safety of both

treatment arms (e.g., complications of multimodal neuronavigation guiding precise bypass surgery) to ensure that the study meets the highest standards of ethics and patient safety. Using guidelines established by the committee and the principal investigators before the study begins, the DSMB may recommend termination of the study if one treatment arm is found to be unequivocally more efficacious than the other or if one of the treatment arms is found to be unsafe. Additionally, the DSMB may recommend modifications to the protocol if a reversible safety issue is identified. A letter including written recommendations and their rationale will be provided to the Chairs of the Steering Committee immediately after each DSMB meeting. This letter will be provided to the central IRBs at their request.

Committee member: ky-2018-3-16

23. Study Drug Supply and Accountability

The study product including aspirin will be purchased by study patients. All study drug supplies in the study will be stored in a secure, safe place, under the responsibility of the Investigator or other authorized individual, and under the conditions described on the labeling.

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product will be responsible for ensuring that the Investigational Product used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All Investigational Product shall be dispensed in accordance with the Investigator's prescription, and it is the Investigator's responsibility to ensure that an accurate record of Investigational Product issued and returned is maintained.

Any quality issue noticed with the receipt or use of an Investigational Product (labeling, expiry date, etc.) should be promptly reported to the Sponsor, who will initiate a complaint procedure.

Under no circumstances will the Investigator supply study Product to a third party, allows the study Product to be used other than as directed by this Clinical Trial Protocol, or dispose of study Product in any other manner.

24. Regulatory Requirements

The study will be conducted in accordance with the China Food and Drug

Administration (CFDA) and Good Clinical Practice.

Each investigator will sign an Investigator Agreement. Protocol amendments are not allowed by any investigator without prior approval from the Sponsor-Investigator. All changes to the protocol should be submitted to the site's IRB for review and approval as appropriate.

25. Institutional Review Board/Independent Ethics Committee(IRB/IEC)

The Investigator or the Sponsor must submit this Clinical Trial Protocol to the central IRB located at Peking University International Hospital, and is required to forward to the Sponsor a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The following information should be clearly stated on the written approval/favorable opinion: the Clinical Trial information (study number, Clinical Trial Protocol title and version number), the documents reviewed (Protocol, Informed Consent Form, Investigator's Brochure, etc.), the list of voting members along with their qualification and the date of the review.

Investigational Product will not be released at the study site and the Clinical Trial will not be initiated until a copy of this written and dated approval/favorable opinion has been received by the Sponsor.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the Ethics Committee (IRB/IEC). It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC).

If requested, a progress report will be sent to the Ethics Committee (IRB/IEC) annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

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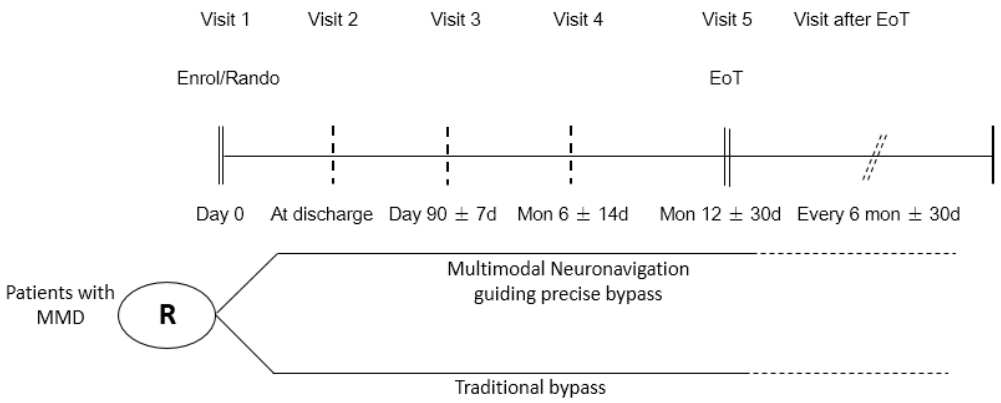
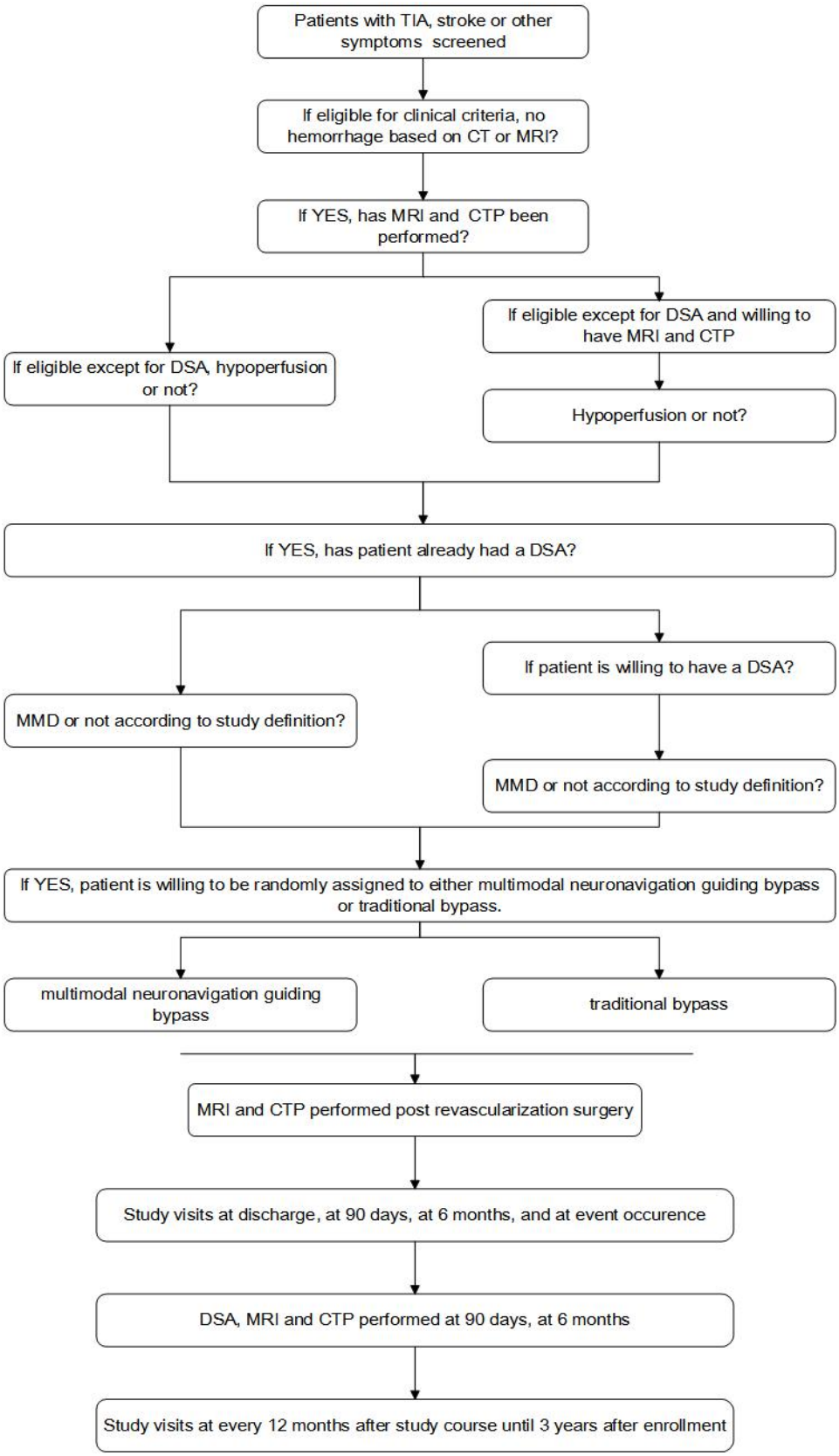
APPENDIXS

Study Design Chart



Study Flow Chart



Schedule of Visits and Tests

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits after 1 year	Event visit
Assessments	**Screening/Randomize**	**At discharge**	**At Day 90 ±7d**	**At Day 6 months ±14**	**At 1 year ± 1 month**	**Every 12 months ±1 month**	
Informed Consent	X						
Eligibility criteria	X						
Patient Randomization	X						
Relevant medical history	X						
Demographics	X						
MRI	X						
CTP	X						
DSA before Surgery							
Vital signs	X						X
Modified Rankin Score	X	X	X	X	X	X	X
NIHSS	X	X	X	X	X		X
Modified Barthel Score	X	X	X	X	X		X
Process Core Labs	X						
MRI after surgery		X	X	X	X		
CTP after surgery		X	X	X	X		X
DSA after surgery		X	X	X			X
Compliance reminder			X	X	X	X	X
Current Medications	X	X	X	X	X	X	X
Risk factor Management	X		X	X	X	X	X
AEs, SAEs and Endpoints		X	X	X	X	X	X

Definition of End Points

Stroke	Sudden symptoms and signs of focal disturbance of cerebral function associated with cerebral circulation disorders..
Ischemic stroke	An acute focal infarction of the brain or retina. Criteria: (1) acute onset of a new focal neurological deficit with clinical or imaging evidence of infarction lasting more than 24 hours and not attributable to a non-ischemic etiology (not associated with brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease); or (2) acute onset of a new focal neurological deficit and not attributable to a non-ischemic etiology lasting less than 24 hours, but accompanied by neuroimaging evidence of new brain infarction; or, (3) rapid worsening of an existing focal neurological deficit lasting more than 24 hours and not attributable to a non-ischemic etiology, and accompanied by new ischemic changes on brain MRI or CT, and clearly distinct from the index ischemic event.
Hemorrhagic stroke	An acute extravasation of blood into the brain parenchyma or subarachnoid space with associated neurological symptoms.
TIA	A neurological deficit of sudden onset, resolving

	completely, attributed to focal brain or retinal ischemia without evidence of associated acute focal infarction of the brain. Criteria: rapid onset of a focal neurological deficit that is without evidence of acute focal infarction of the brain, and is not attributable to a non-ischemic etiology (brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease)
Symptomatic intracerebral hemorrhage	Any extravascular blood in the brain associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration. Intracerebral hemorrhage is defined as an acute extravasation of blood into the brain parenchyma. Criteria: evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery, or autopsy
Asymptomatic intracerebral hemorrhage	an acute extravasation of blood into the brain parenchyma without clinical deterioration. Criteria: evidence of hemorrhage in the brain parenchyma demonstrated by head imaging, surgery or autopsy
Other symptomatic intracranial hemorrhage	Any extravascular blood within the cranium associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic

	deterioration. Other Intracranial Hemorrhage is defined as an acute extravasation of blood into the subarachnoid space, epidural space, or subdural space with associated symptoms. Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy
Other Asymptomatic intracranial hemorrhage	An acute extravasation of blood into the subarachnoid space, epidural space, or subdural space without associated symptoms. Criteria: evidence of hemorrhage in the subarachnoid space, epidural space, or subdural space demonstrated by head imaging, surgery, or autopsy
Ischemic vascular death	Death due to ischemic stroke, myocardial infarction, sudden cardiac death, arrhythmia, pulmonary embolism, bowel or limb infarction, or any death not readily attributable to a non-ischemic cause
Hemorrhagic Vascular death	Death due to intracranial or systemic hemorrhage

modified Barthel Scale

	Independent	Need some help	Need more help	Totally dependent
Feeding	10	5	0	
Bathing	5	0		
Grooming	5	0	-	-
Dressing	10	5	0	-
Bowel control	10	5	0	-
Bladder control	10	5	0	-
Toileting	10	5	0	-
Chair transfer	15	10	5	0
Ambulation	15	10	5	0
Stair climbing	10	5	0	-
Items are rated based on the amount of assistance required to complete each activity Score ____				

modified Rankin Scale

The modified Rankin Scale (mRS) is a scale commonly used for measuring the degree of disability or dependence in the daily activities of individuals who have suffered a stroke, and it has become the most widely used clinical outcome measure for stroke clinical trials.	
Description	**Score** (select one)
No symptoms at all	**0** ☐
No significant disability despite symptoms; able to carry out all usual duties and activities	**1** ☐
Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	**2** ☐
Moderate disability; requiring some help, but able to walk without assistance	**3** ☐
Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	**4** ☐
Severe disability; bedridden, incontinent and requiring constant nursing care and attention	**5** ☐

NIH Stroke Scale

Administer stroke scale items in the order listed. Record the performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	**Scale Definition**	**Score**
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.	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 flexic.	_____
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 cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____

Instructions	Scale Definition	Score
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.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
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 contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____
3. Visual: 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.	**0 = No visual loss.** **1 = Partial hemianopia.** **2 = Complete hemianopia.** **3 = Bilateral hemianopia** (blind including cortical blindness).	_____

Instructions	Scale Definition	Score
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.	**0 = Normal**symmetrical movements. **1 = Minor paralysi**s (flattened nasolabial fold, asymmetry on smiling). **2 = Partial paralysis** (total or near-total paralysis of lower face). **3 = Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____

Instructions	Scale Definition	Score
5. Motor Arm: 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 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.	**0 = No drift**; limb holds 90 (or 45) degrees for full 10 seconds. **1 = Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. **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. **3 = No effort against gravity**; limb falls. **4 = No movement.** **UN** = Amputation or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____

Instructions	Scale Definition	Score
6. Motor Leg: 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.	**0 = No drift;** leg holds 30-degree position for full 5 seconds. **1 = Drift;** leg falls by the end of the 5-second period but does not hit bed. **2 = Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. **3 = No effort against gravity;** leg falls to bed immediately. **4 = No movement.** **UN** = Amputation or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____ _____
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 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.	**0 = Absent.** **1 = Present in one limb.** **2 = Present in two limbs.** **UN = Amputation or joint fusion**, explain: _____	_____

Instructions	Scale Definition	Score
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.	**0 = Normal;** no sensory loss. **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. **2 = Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____

Instructions	Scale Definition	Score
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.	**0 = No aphasia;** normal. **1 = Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. 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. **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. **3 = Mute**, global aphasia; no usable speech or auditory comprehension.	_____

Instructions	Scale Definition	Score
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.	**0 = Normal.** **1 = Mild-to-moderate dysarthria**; patient slurs at least some words and, at worst, can be understood with some difficulty. **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. **UN = Intubated** or other physical barrier, explain:_____	_____
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.	**0 = No abnormality.** **1 = Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. **2 = Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____
	Total NIHSS:	_____