Project Source: National Key R&D Program of China Reperfusion Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke (Project Number: 2016YFC1301500)

Endovascular treatment key technique and emergency work flow improvement of acute ischemic stroke, ANGEL-ACT

— A prospective, multi-center, registry study

Clinical Study Protocol

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Study Sponsor:	Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China
Study Period:	July 2017-December 2020
Protocol version:	V1.0 /July 1, 2017

Protocol Synopsis

Study Title	Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic stroke, ANGEL-ACT- A Prospective Multicenter Registry Study
Responsible Party	Beijing Tiantan Hospital, Capital Medical University
Study Center	111 centers in China
Study Objectives	To determine the current status of endovascular treatment (EVT) of acute ischemic stroke in China and the key element of treatment delay, explore key appropriate technology, develop standards and paths which shorten delays and increase efficiency to improve the efficiency of first aid, shorten the treatment time, and improve clinical prognosis.
Study Design and Funding Source	This study is a multi-center, prospective registry study initiated by researchers, funded by National Key R&D Program of China.
Study Population	A total of 2,000 patients with acute ischemic stroke will undergo endovascular treatment.
Inclusion Criteria	1. Age ≥ 18 years old; 2. Diagnosis of acute ischemic stroke; 3. Imaging confirmed intracranial large artery occlusion (LVO): intracranial internal carotid artery (ICA T/L), middle cerebral artery (MCA M1/M2), anterior cerebral artery (ACA A1/A2), basilar artery (BA), vertebral artery (VA V4), and posterior cerebral artery (PCA P1); 4. Initiation of any type of endovascular treatment (EVT), including intra-arterial thrombolysis, mechanical thrombectomy, angioplasty, and stenting; 5. The patient or the patient's legal representative is able and willing to sign the informed consent.
Exclusion Criteria	1. Isolated cervical ICA or VA occlusion; 2. No evidence of LVO on DSA.
Follow-up Plan	Baseline, immediately after the procedure (within 2 hours), 24 hours after the procedure, 7 days after the procedure or at discharge, 90 days after the procedure.
Efficacy Objectives	● **Primary Efficacy Endpoint:** ➢ Functional independence at 90 days (defined as mRS≤2) ● **Secondary Efficacy Endpoints:** ➢ Recanalization rate at the end of the procedure (mTICI score 2b-3) ➢ Recanalization rate after the first attempt (mTICI score 2b-3) ➢ Changes in NIHSS score immediately after the procedure ➢ Changes in NIHSS score 24h after the procedure ➢ Changes in NIHSS score 7 days after the procedure or at discharge

	➢ Quality of life evaluation at 90 days (EQ-5D, BI)
Safety Objectives	● **Primary Safety Endpoint** ➢ Symptomatic intracranial hemorrhage (sICH) with 12-36 hours after the procedure ● **Secondary Safety Endpoints** ➢ Parenchymal hematoma (PH2) ➢ Any intracranial hemorrhage on imaging within 12-36 hours after the procedure ➢ All-cause mortality within 90 days
Efficiency Objectives	● **Primary Efficiency Endpoint** ➢ Time from symptom onset to recanalization (min) ● **Secondary Efficiency Endpoints** ➢ Time from onset to admission(min) ➢ Time from admission to imaging(min) ➢ Time from imaging to puncture(min) ➢ Time from puncture to recanalization (min)
Study Period	July 2017-December 2020

Signature Page

Study Responsible Party: Beijing Tiantan Hospital, Capital Medical University

Principal Investigator:

I participate in this clinical study and will seriously perform the duties of a researcher in accordance with ICH-GCP regulations.

I have read this protocol and this study will be conducted in accordance with the moral, ethical and scientific principles prescribed in the Declaration of Helsinki and the China GCP.

Principal Investigator (Signature):

Date: Saturday, July 01, 2017

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Abbreviations and Terms

Abbreviations and Terms	Definitions
AE	Adverse Event
AIS	Acute Ischemic Stroke
ASPECT	Alberta Stroke Program Early CT score
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
ALP	Alkaline Phosphatase
CT	Computed Tomography
CRF	Case Report Form
CFDA	China Food and Drug Administration
CRP	C Reactive Protein
CRC	Clinical Research Coordinator
CEC	Clinical Events Committee
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
DSMB	Data Safety Monitoring Board
DALY	Disability Adjusted Life Year
DRQ	Data Request Queue
DVP	Data Verification Plan
DILI	Drug Induced Liver Injury
EQ-•5D	EuroQol Five Dimensions Questionnaire
EDC	Electronic Data Capture
GCP	Good Clinical Practice
HR	Hazard Ratio
IEC	Independent Ethics Committee
ID	Identification
LOCF	Last Observation Carried Forward
LFU	Loss to Follow-Up
mRS	Modified Rankin Scale
MRI	Magnetic Resonance Imaging
NIHSS	National Institute of Health Stroke Scale
OR	Odds Ratio
PHL	Potential Hy's Law
Rt-•PA	Recombinant Tissue Plasminogen Activator
SAS	Safety Data Set
SAE	Serious Adverse Event
SDV	Source Data verification
TXB-2	Thromboxane B 2
TBL	Total Bilirubin
UAT	User Acceptance Test
ULN	Upper Limit of Normal

Text

1. Study Background

On October 25, 2015, the Chinese Stroke Association published the China Stroke Epidemic Report (2015). Data shows that stroke is ranked first in top three diseases that threaten human health and has become the first cause of mortality for residents in China. One person gets sick every 12 seconds, and one person dies of the disease every 21 seconds. About 1.3 million patients die of cerebrovascular disease every year in China. Among the new stroke cases each year, 12% are under the age of 45, showing a younger trend. At present, there are more than 7 million patients with cerebrovascular disease in China, of which about 70% are ischemic strokes.

Studies have shown that 40-50% of patients with acute ischemic stroke are due to large vessel occlusion.[1] Early recanalization of occluded vessels to regain the blood flow in brain tissue in the ischemic area can reduce further damage to brain tissue in the ischemic penumbra and improve the prognosis. 20 years ago, intravenous tPA thrombolysis was initially approved for ischemic stroke within 3 hours of the onset.[2] However, intravenous alteplase appears to be much less effective at opening proximal occlusions of the major intracranial arteries. [3] Early recanalization after intravenous alteplase is seen in only about one third of patients with an occlusion of the internal-carotid-artery terminus, [4] and the prognosis without revascularization is generally poor for such patients.[5] For these reasons, intraarterial treatment is regarded as a potentially important component of the therapeutic armamentarium.

The New England Journal of Medicine recently published positive results of five randomized controlled trials successively, [6-10] and the main conclusions are: (1) rapid reperfusion is the key to a good prognosis; (2) endovascular stent thrombectomy is safe and effective; (3) neuroimaging is critical to patient selection; (4) teamwork is the key to success. China, the United States and Europe have also released the latest guidelines, presenting clinical reference standards. Endovascular treatment mainly with stent retriever has become the main solution for acute large vessel occlusion. However, for Chinese population in real world, how to effectively give first aid of endovascular treatment for acute ischemic cerebrovascular disease according to the guidelines? How to improve the first aid workflow and select appropriate key technology for treatment? All these problems need to be solved urgently.

We plan to integrate the advantage and strength of the China Stroke Center Alliance Acute Ischemic Stroke Endovascular Treatment Collaboration Group on the research network platform of China Stroke Association to evaluate the utilization, and subsequent outcomes of endovascular treated acute ischemic stroke in China through a prospective multicenter registry study. Moreover, study will analyze the key element that causes the first aid delay in the workflow for the endovascular treatment of acute ischemic stroke and discuss the key appropriate technology for endovascular treatment of acute ischemic stroke.

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2. Study Subjects

2.1 Number of planned study subjects

A total of 2000 cases are planned to be enrolled.

2.2 Inclusion criteria

1). Age ≥ 18 years old;

2). Diagnosis of acute ischemic stroke;

3). Imaging confirmed intracranial large artery occlusion (LVO): intracranial internal carotid artery (ICA T/L), middle cerebral artery (MCA M1/M2), anterior cerebral artery (ACA A1/A2), basilar artery (BA), vertebral artery (VA V4), and posterior cerebral artery (PCA P1);

4). Initiation of any type of endovascular treatment (EVT), including intra-arterial thrombolysis, mechanical thrombectomy, angioplasty, and stenting;

5). The patient or the patient's legal representative is able and willing to sign the informed consent.

2.3 Exclusion criteria

1). Isolated cervical ICA or VA occlusion;

2). No evidence of LVO on DSA.

3. Study Objectives

To clarify the current status of endovascular treatment of acute ischemic stroke in China. To explore key technology, develop norms and paths to shorten delays and improve clinical prognosis.

3.1 Efficacy Objectives

3.1.1 Primary efficacy endpoint:

Functional independence at 90 days (defined as mRS≤2)

3.1.2 Secondary efficacy endpoints:

1） Recanalization rate at the end of the procedure (mTICI score 2b-3) 2）

Recanalization rate after the first attempt (mTICI score 2b-3)

3） Changes in NIHSS score immediately after the procedure 4）

Changes in NIHSS score 24h after the procedure

5） Changes in NIHSS score 7 days after the procedure or at discharge 6）

Quality of life evaluation at 90 days (EQ-5D， BI)

3.2 Safety objectives

3.2.1 Primary safety endpoint:

Symptomatic intracranial hemorrhage (sICH) within 12-36 hours after the procedure

3.2.2 Secondary safety endpoints:

1） Parenchymal hematoma (PH2)

2） Any intracranial hemorrhage on imaging within 12-36 hours after the procedure

3） All-cause mortality within 90 days

3.3 Efficiency objectives

3.3.1 Primary Efficiency objective：

Time from symptom onset to recanalization (min)

3.3.2 Secondary Efficiency objectives：

1) Time from onset to arrival(min)
2) Time from arrival to imaging(min)
3) Time from imaging to puncture(min)
4) Time from puncture to recanalization (min)

3.4 Other study objectives

1) Health economics assessment (cost-benefit analysis);
2) A stratification analysis of the effects of age, gender, baseline NIHSS score, ASPECT score, occlusion site, blood pressure, hypertension, diabetes, etiology classification, treatment method, collateral circulation, materials, antithrombotic drugs, anesthesia protocol, whether or not recanalization, etc. on the outcomes

4. Study design

4.1 Study type

A prospective, multi-center, registry study

4.2 Follow-up visit timing

Baseline, immediately after the procedure (within 2 hours), 24±3 hours after the procedure, day 7±2 or discharged, day 90±7

5. Research plan and workflow

Overall study period: July 2017-December 2020

Subject study period: 90 days

The end of the entire study was defined as "the last follow-up visit of the last subject in the study"

6. Visit schedule

Measure	Baseline	Immediately after the procedure (within 2h)	24 hours after the procedure	Day 7±2 or discharge	Day 90
Demographic characteristics	X				
Current medical conditions collection	X				
mRS	X				X
Past medical history	X				
Drug treatment	X	X	X	X	X
GCS	X*	X*	X*	X*	
NIHSS	X	X	X	X	
Blood pressure	X	X	X		
Head CT/MRI	X	X	X***		
ASPECT score	X				
Laboratory examination	X**				
Electrocardiogram	X				
Verify inclusion/exclusion criteria	X				
Sign informed consent form	X				
Head CTA	X				
TOAST Classification				X	
EQ-5D rating scale					X
BI Index					X
Complications related to the procedure		X			
AE/SAE		X	X	X	X

Notes on study imaging examination:
1. All patients need to complete plain CT scan before the procedure (baseline). The examination method of Plain CT scan+ CTA is recommended for patients with anterior circulation arterial occlusion, and magnetic resonance imaging (MRI+MRA) is recommended for patients with posterior circulation arterial occlusion. If it is unable to perform priority examination due to the limitation of central conditions, the imaging evaluation of brain tissue and blood vessels can be completed according to the actual situation.
2. The head plain CT scan must be completed 24 ± 3 hours after the procedure. If conditions permit, magnetic resonance imaging (MRI + MRA) can be performed; the head CTA is preferred to evaluate the vascular recanalization, if feasible TCD cannot be completed for evaluation. If MRA has been performed, CTA or TCD is not required.
* Required only for patients with posterior circulation stroke
** Including: blood routine (including white blood cell count, neutrophil count, hemoglobin, platelet count, etc.), blood coagulation, blood glucose, hepatic and renal function (including serum creatinine, serum transaminase, etc.).
*** Could be taken 12-36 hours after the procedure.

6.1 Visit 1 (Baseline)

Before enrollment, patients or their relatives should fully obtain written and oral instructions about the study and sign written informed consent.

- Review inclusion/exclusion criteria

- Sign informed consent form
- Ask about demographic data
- Ask about related medical and surgical history
- Vital signs and physical examination
- 12-lead electrocardiogram
- CT, CTA (CTP) or MRI (including MRA)
- ASPECT, NIHSS, modified Rankin scale, GCS (posterior circulation stroke)
- Laboratory examination
- Record medication before onset
- Intravenous thrombolysis and endovascular treatment

The results of the examination conducted in Visit 1 was taken as the baseline value.

6.2 Visit 2 (Immediately after the procedure (within 2h))

- Blood pressure
- NIHSS, GCS (posterior circulation stroke)
- Plain CT scan
- Complications related to the procedure
- AE/SAE

6.3 Visit 3 (24±3 hours after the procedure)

- NIHSS, GCS (posterior circulation stroke)
- Blood pressure
- Head CT or MRI (12-36 hours)
- AE/SAE

6.4 Visit 4 (7±2 days after the procedure or discharged)

- NIHSS, GCS (posterior circulation stroke)
- TOAST Classification
- Medication
- AE/SAE

6.5 Visit 5 (Day 90±7)

The 90-day follow-up will be ascertained using a standardized telephone interview performed by trained investigators blinded to the baseline and procedural data.

- Modified Rankin Scale score
- EQ-5D scale score
- BI Index
- Medication
- AE/SAE

6.6 Visits in need

- When the patient has an aggravation of nerve defect symptoms at any time point, NIHSS and GCS (posterior

circulation) evaluation shall be performed, and plain CT scan should be completed. MRI can be performed according to the situation.

- Patients who have any adverse events or serious adverse events should be visited until it is relieved or disappear.

7. Withdrawal and Elimination

7.1 Withdrawal decided by investigators

The investigator decided to withdraw the case from the study when the selected subjects had the following conditions during the study.

1) No endovascular treatment was performed for any reason;
2) Other unsuitable conditions to continue the study in the opinion investigators.

7.2 Subjects voluntary withdrawal

According to the provisions of the informed consent, the subject has the right to withdraw from the study halfway, or refuse to receive follow-up.

7.3 Elimination

Subjects who should not be enrolled but who have been enrolled, or who have completed the study, but violated certain provisions of the study protocol during the study, should be eliminated from the study, including:

1) Do not meet the inclusion criteria;
2) The missing of the main variables >30%

The principal investigator and statistician decide whether the cases are eliminated. The reason should be given for the eliminated cases, and their study medical records should be kept for future reference.

8. Endovascular treatment

8.1 Anesthesia

Local anesthesia was recommended, using conscious sedation when necessary. General anesthesia should be used if the patient is expected to cooperate poorly during surgery even with the use of conscious sedation, or the use of conscious sedation is at high risk, or with high-risk airway conditions.

8.2 Endovascular treatment

The local interventionalist decides what techniques to be used for the endovascular treatment and when to stop the endovascular recanalization procedure or to undertake further recanalization attempts. The treatment methods included stent-retriever thrombectomy, aspiration thrombectomy, intra-arterial thrombolysis, angioplasty and/or stenting.

8.3 Postoperative antithrombotic medications

The investigators of the sub-sites selected a reasonable antithrombotic treatment according to the type of etiology, intraoperative operation and postoperative images of the patients.

9. Imaging Core Laboratory

A core laboratory will perform assessments for images of all subjects. The assessments will be performed by readers who are blinded to all clinical findings. All sites should provide imaging that is suitable for analysis. Radiologic assessment included early ischemic changes on CT using Alberta Stroke Program Early CT Score

(ASPECTS) for anterior circulation strokes, the posterior circulation–ASPECTS (pc-ASPECTS) for posterior circulation strokes, location of occlusion site, presence of underlying ICAD (defined as fixed stenosis degree >70% or stenosis >50% with distal blood flow impairment or evidence of repeated re-occlusion), baseline and post-procedural mTICI, tandem occlusion (T/O), and occurrence of ICH on post-treatment CT. Angiographic success was defined as achieving modified Thrombolysis in Cerebral Infarction scores of 2b (≥50% reperfusion) or 3 (complete reperfusion)

10. Quality control

10.1 Preservation and monitoring of source data/documents

Original documents are the basis for the actual existence of subjects and the credibility of the collected data. Original documents should be kept at each study site.

The data on the case report form are from the source documents, which should be consistent with the source documents. If there is any discrepancy, the reasons should be explained.

The following data recorded in the case report form should be derived from the source documents:

- General information of subjects (initials, gender, date of birth, height and weight)
- Date of subject's participation in the study

  Date of subject follow-up

  Medical history (concomitant disease, start, end, change)
- Medication history (concomitant treatment and medication taken, start, end, change)
- Adverse events (occurrence, end, change of adverse events)
- Serious adverse event (occurrence, end, change of SAE)

  Laboratory Test Results
- ECG results and results of other medical instrument examinations

All other data (i.e., no written or electronic record of data) can be directly recorded on the eCRF and recognized as source data.

The investigator must allow the sponsor to conduct monitoring, audit, review by the Ethics Committee and inspection by relevant regulatory authorities, and allow the above personnel to consult all relevant source data/documents.

10.2 Site personnel training

Before the first study subject is enrolled in the study, the sub-site investigators will receive standardized training and assessment, and the sub-site study can be initiated only after the assessment is passed. The principal investigator should ensure that all study personnel receive the training. The principal investigator will maintain a record of all study related personnel (physicians, nurses, and others).

10.3 Study monitoring

During the study, the clinical research associate (CRA) will perform the on-site monitoring visit to the study hospital regularly to ensure that all contents of the study protocol are strictly followed, and check the source data to ensure the consistency with the contents on the eCRF. The study site will retain all source records and source data.

The investigators should truthfully, in detail and carefully record the contents in the eCRF. All observations and findings in the study should be verified to ensure the reliability of the data and that all conclusions are derived from the source data.

11. Adverse events

11.1 Definition of adverse events

Any adverse medical events during the period from enrollment to the last follow-up of a patient, regardless of relationship with the treatment, will be judged as an adverse event. In a clinical study, any unexpected occurrence event in a subject is an adverse event. The study doctor should report all adverse events directly observed by the physician or spontaneously reported by the subject in concise medical terminology. The occurrence time, severity, duration, measures taken and outcome of adverse events were recorded.

11.2 Observation and recording of adverse events

All of the following events were recorded for all patients: adverse events (AEs), serious adverse events (SAEs), death, recurrent stroke, laboratory abnormalities, vital sign changes, etc. Adverse events were recorded from the start of enrollment until 90 days or last follow-up. If an adverse event occurs, it will be followed until the adverse event disappears or returns to the baseline level or is not clinically significant.

All adverse events occurring during the study will be recorded in the eCRF. The evaluation of adverse events includes the name, severity, outcome and treatment measures of adverse events.

11.3 Severity of adverse events

The severity of adverse events is classified into three levels: mild, moderate and severe, which are defined as follows:

1) Mild – Mild symptoms or disease that resolve soon after drug discontinuation and do not require treatment.
2) Moderate – Results in temporary impairment, does not require hospitalization or prolongation of existing hospitalization, requires treatment or intervention, and is easily reversible.
3) Severe - Transient impairment, requiring inpatient hospitalization for outpatients and prolonged hospitalization (more than 7 days) for inpatients, or causing permanent system/organ damage, or life-threatening (e.g., asphyxia, shock, coma and other symptoms requiring first aid).

11.4 Serious adverse events

A serious adverse event is defined as an adverse event that:

1) Results in death;
2) Is life-threatening (refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to those adverse events that may cause death if the hypothetical situation is more serious);
3) Requires or prolongs patient hospitalisation;
4) Results in persistent or significant disability or incapacity;
5) Results in a congenital anomaly or birth defect;
6) A medical event that, in the opinion of the investigator, could be judged to be a serious adverse event.

If a subject develops any serious adverse event during the study, the investigator should immediately take

appropriate treatment measures for the subject to ensure the safety of the subject. The investigator must report to the monitor, the Ethics Committee of the site and the undertaker within 24 hours. The undertaker shall report to the Ethics Committee and sponsor, and simultaneously report to China Food and Drug Administration for filing. The investigator must complete the SAE form.

Serious adverse events that are unresolved at the end of the study or early withdrawal of a subject must be followed up until one of the following conditions is met:

1) Event disappeared or resolved
2) Event stable
3) Event returned to baseline (if baseline value available)
4) Event resolved to not clinically significant
5) When more information is unlikely to be available (the patient or medical staff refuses to provide more information, or there is evidence that the patient is still lost to follow-up after the best efforts have been made).

11.5 Recording, handling and reporting

1) Any adverse events occurring during the study should be documented.
2) All adverse events must be handled carefully.
3) The investigator was to avoid induced questioning. While observing the efficacy, pay close attention to the observation of adverse events or unexpected toxic and side effects (including symptoms, signs and laboratory tests), analyze the causes, make a judgment, and follow up the observation and recording.
4) The incidence of adverse events shall be statistically analyzed.
5) For adverse events occurred during the trial, the symptoms, severity, occurrence time, duration, treatment measures, outcome and follow-up methods should be recorded in the eCRF in detail, and signed and dated
6) The investigator should decide whether to terminate the trial or not according the disease conditions if there is any adverse event. Follow-up investigation is required for the patient who discontinued the drug administration due to adverse event. The handling process and results should be recorded in detail.
7) Once serious adverse events or important adverse events occur in the study, the investigator must initiate emergency procedures.

12. Ethical and regulatory requirements

Ensure the safety and privacy of the subjects; supervise the ethics, informed content, etc. of the study.

12.1 Approval of the independent ethics committee (IEC)

According to local regulations, all protocols (and relevant amendments, if any), including patient information sheet and informed consent form, must be approved by the corresponding IEC before implementation. Relevant reports on registry progress will be submitted to IEC by investigator or sponsor, including notifying IEC of the completion or termination of registry.

12.2 Patient information sheet and informed consent form

These documents will be created in accordance with ICH-GCP guidelines and will be made available to the Ethics

Committee as independent documents. Only approved versions will be used for this registry.

When obtaining and recording informed consent, investigator must comply with relevant local regulatory requirements and abide by requirements of ICH-GCP guidelines and Declaration of Helsinki.

Before carrying out registry-related activities, investigator must verbally describe the information about this registry to the subjects and provide written information about this registry in a form that the subjects can read and understand.

Informed consent forms must be signed and dated voluntarily by the subjects or their relatives before the registry-related activities are carried out. Written informed consent must be signed and dated by the person responsible for implementing the informed consent procedure.

Patients participating in this registry will be informed that they can refuse to participate in the study, which will not affect their medical care. Information on their medical conditions will be collected and recorded, and all findings will be processed under strict confidentiality. The written informed consent of all patients will be collected before being enrolled in this registry.

Copies of patient information sheet and informed consent form will be provided to patients.

12.3 Required documents

The following documents must be inspected by the sponsor.

1) The latest resumes of principal investigator.
2) The signed investigator page in the protocol.
3) Copies of dated IEC certification and approval documents for the protocol and local investigators, including any amendments, patient information sheets and informed consents, patient compensation (if any) and any other submitted documents. The IEC approval document should indicate the version No. and/or date of the document under review.
4) The signed contract between the sponsor and the study center.
5) The local hospital management approval documents (when necessary) (scientific research department).
6) All other relevant documents required before the initiation of registry should be properly placed in the master registry document.

13. Data management

13.1 Data collecting methods-filling and transferring of electronic case report form (eCRF)

eCRF should be filled in by the investigator. Each enrolled case should complete the eCRF. All eCRFs are collected by electronic data capture (EDC) of the National Clinical Research Center for Neurological Diseases, and all data are submitted to the data administrator for data management after being reviewed by clinical research associate (CRA).

13.2 Steps and tasks of data management

1) Design of eCRF and database

The design of eCRF should ensure that all data specified in the protocol and meeting the statistical analysis requirements are collected, and a filling guideline should also be established for the corresponding eCRF.

Logical verification should be designed according to the design instructions of the database. The database can be

used after the User Acceptance Testing (UAT) is qualified.

2) Reception of data

The data collection and management in this study all follow the requirements of GCP. Data administrator designated by the statistical unit should be responsible for the data collection and management. Data administrator should compile the data collection program to collect and manage the data.

The investigator or Clinical Research Coordinator (CRC) should fill in the eCRF accurately, timely, completely and regularly according to the eCRF filling guidelines. Data collection instructions should be formulated to determine the requirements and methods of data collection. The sending, transferring and reception of CRF should be carried out as per the standard operating procedures.

For doubts existed in the eCRF, data administrator should generate Data Request Queue (DRQ) and make inquiry to investigator via CRA. The investigator should answer as soon as possible and return the DRQ. Data administrator should modify and confirm the data according to the answers of investigator. DRQ can be issued again if necessary.

3) Data validation and clarification

Data administrator, CRA, medical personnel and statisticians should conduct data validation according to the data validation contents.

4) Medical coding

Coding standards, procedures and dictionaries should be established and ICD-10 and WHO ATC should be adopted to match adverse events, medical diagnosis, concomitant medication, previous medication, previous medical history and other descriptions collected from eCRF.

5) External data management

For the management of external data such as laboratory data, electronic log, ePRO, randomization, etc., quality control of external data is carried out through data transmission protocol, including data type, data provider, data format, transmission mode, transmission frequency, etc.

6) Database locking, unlocking and re-locking

Process, responsible person and SOP document for database locking are established. The conditions and process for unlocking and re-locking after database locking are stipulated.

7) Data export and transmission

The data export and transmission file format, export contents (database, variable name and variable value code), submission procedures and transmission medium should be described and should conform to the requirements of national regulations and regulatory authorities.

8) Archiving requirements for data and data management documents

The trial data, the time of entry/import into the database, the entry person, the data audit trail and the

documents formed in the data management process need to be completely saved. The data formed in the data management process usually include but are not limited to clinical trial data, external data, database metadata information, reference value range for laboratory tests, logic tests and change control lists of derived data, data clarification forms, program codes, etc. Documents formed in the data management process usually include but are not limited to: data management plan, blank CRF, CRF filling guideline, PDF format document for completing CRF, annotation CRF, database design description, database entry description, data validation plan, data quality control validation report, etc.

The data management plan should specify the trial data to be archived, management documents, media, archiving method and time limit.

13.3 Data quality management

The data management plan should determine the quality control items, quality control methods (such as quality control frequency, sample selection method and sample size, etc.), quality requirements and standards, and remedial measures for failing to meet the expected quality standards, etc. of the data and data management operation process.

14. Statistical analysis and sample size

The statistical analysis of the study is completed by a third party. The EDC system of the National Clinical Medical Research Center for Neurological Diseases is adopted for data management and SAS9.4 software is used for data statistical analysis.

14.1 Statistical analysis

The section provides a general description of the statistical plan for the analysis of study data. An extensive version of the analysis plan will be finalized before the database is locked.

Patients will be described with respect to demographics (including gender and age) and baseline characteristics. Treatment and procedural characteristics will be described. In general, summaries will be presented by anterior and posterior circulation. Descriptive statistics for dichotomous/categorical variables will include number and percent of subjects in each category (including missing). Descriptive statistics for continuous variables will include number of missing subjects, lower quartile, median, upper quartile, or mean, and standard deviation, as appropriate.

The primary and secondary endpoints will be reported. The outcomes will be compared between patients with different subgroups. Logistic regression will be performed to explore variables associated with good functional outcome. Adjusted odds ratios (aOR) with their 95% confidence intervals (CI) will be calculated.

14.2 Interim analysis

No interim analysis will be conducted in this study.

14.3 Handling of missing data

Patients will be truncated to the earlier of the following two dates: the end-of-treatment visit and the last study contact date when all components of the endpoint of interest in this study have completed the evaluation. For endpoints that do not include death, all death events are censoring events. Unless the patients exercise the right to revoke informed consent, the complete endpoint information of all patients should be traced as far as

possible. Patients with non-fatal events will continue to receive study follow-up.

15. Protocol revision principle

All revisions to the protocol must be signed and recorded by all signatories to the original protocol.

16. Confidentiality principle

The personal disease information of the subject obtained in the study is regarded as confidential and is forbidden to be disclosed to a third party except for the following circumstances. The patient's condition is further protected by using the subject identification code:

1) Relevant disease information can be provided to the subject's responsible physician or other relevant physicians.
2) Relevant data and materials of this trial can be provided to the following personnel for reference, including participating physicians, representatives of sponsor, ethics committees and relevant regulatory agencies.

17. Paper publication

All the institutions and individuals that have the right to share the research data must follow the publishing requirements of the sponsor. All institutions and individuals must submit the papers to the sponsor and the principal investigator before publishing, and the investigator will review them to ensure the quality of the data and statistical results.

Appendix 1: Study Definitions

Symptomatic Intracranial Hemorrhage (sICH, Heidelberg Bleeding Classification): new intracranial hemorrhage detected by brain imaging associated with ≥4 points total National Institutes of Health Stroke Scale (NIHSS), ≥2 points in one NIHSS category, leading to intubation/ hemicraniectomy/ EVD placement or other major medical/surgical intervention, or absence of alternative explanation for deterioration

Parenchymal Hemorrhage (PH): More homogenous areas of hemorrhage, with or without intraventricular extension, usually with mass effect. PH1 is defined as hematoma in <30 % of infarct area. PH2 is defined as hematoma in >30% of infarct area

Subarachnoid Hemorrhage: Bleeding from a ruptured intracranial blood vessel, confined to the subarachnoid space

Intracranial atherosclerotic disease (ICAD): defined as fixed stenosis degree >70% or stenosis >50% with distal blood flow impairment or evidence of repeated re-occlusion

Appendix 2. TOAST Classification Criteria for Ischemic Stroke

In 2005, Hakan, et al. from the United States modified the 1993 version of classic TOAST based on the "STOP Stroke" study, which is called SSS TOAST (Stop Stroke Study-TOAST). The classification still follows the five subtypes of classical TOAST: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology. However, each subtype is divided into different grades according to the amount of clinical, imaging, laboratory examination and previous medical history evidence obtained: evident, probable and possible. It's "evident" if the evidence is sufficient and complete with definite cause. It's "probable" if there are multiple definite causes coexisting and the true cause cannot be determined. It's "possible" if the correlation is weak at present or no direct correlation has been found.

I. Large-artery atherosclerosis

- Evident (meeting all of the following):

– Atherosclerosis induced occlusion or stenosis of intracranial or external arteries related to clinical manifestations ≥50%.

– No acute infarction outside the blood supply area of stenosis or occlusion artery.

- Probable (meeting any of the following):

– There has been one or more transient monocular amaurosis, TIA or stroke in the arterial blood supply area of atherosclerosis in the past month.

– Intracranial or extracranial near occlusive stenosis or non-chronic occlusion related to clinical manifestations is determined to be caused by atherosclerosis.

– There is an ipsilateral internal watershed infarction or multiple infarction limited in the blood supply area of the diseased vessel.

- Possible (meeting one of the following):

– There are two or more attacks of transient monocular amaurosis, TIA or stroke (at least one attack is within one month) in the arterial blood supply area with atherosclerosis in the past. The examination found that intracranial or extracranial arteries related to clinical manifestations have atherosclerotic plaques protruding into the lumen and lead to mild stenosis of the lumen (50%).

– There is definite evidence of atherosclerosis in the absence of a comprehensive examination to exclude other mechanisms.

II. Cardioembolism

- Evident

– There is evidence of high-risk cardiogenic cerebral embolism.

- Probable (meeting one of the following)

– There is evidence of systemic embolism (including pulmonary embolism, mesenteric artery embolism, renal artery embolism or skin embolism, etc.).

– Acute multiple cerebral infarction occurs in left and right anterior circulation or anterior and posterior circulation in time, but no complete occlusion or nearly complete occlusion is found in the responsible blood

vessel; Other possible causes of multiple cerebral infarction, such as vasculitis, vasculopathy, hematopathy or hemodynamic instability, must be excluded.

- Possible (meeting one of the following)

– Evidence of low-risk or uncertain-risk cerebral embolism.

– There is clinical evidence of aortic arch and cardiogenic cerebral embolism, but the evaluation of other etiologies is incomplete.

III. Small-vessel occlusion

- Evident

– The image shows a clinically consistent lesion with a diameter of less than 20mm located in the penetrating artery of the skull base or brainstem. No other pathological changes such as local atherosclerosis, arterial dissection, vasculitis or vasospasm are found in the parent artery from which the perforating artery is originated.

- Probable

– TIAs with the same symptoms occur in the past week, and the symptoms are consistent with stereotypic lacunar TIAs.

- Possible (meeting one of the following)

– Clinically, it is consistent with typical lacunar syndrome, but no consistent lacunar infarction is found on the image.

– There is clinical evidence of arteriolar obstruction, but the evaluation of other etiologies is incomplete.

IV. Stroke of other determined etiology

- Evident

– Confirmation of an etiology that affects brain blood vessels and causes consistent clinical symptoms.

- Probable

– Confirmation of the existence of a disease that has a clear and close relationship with cerebral infarction, such as arterial dissection, cardiac vascular surgery or cardiovascular intervention.

- Possible

– There is clinical evidence of other etiologies, but the evaluation of the etiologies listed above is incomplete.

V. Stroke of undetermined etiology

- No determined etiology (Not meeting the diagnostic criteria of "evident" or "possible" listed above)

– Cryptogenic embolism (meeting any of the following)

- Angiography shows a thrombus in a seemingly normal cerebral vessel causing a sudden complete occlusion.
- There is imaging evidence that a previously completely blocked blood vessel is recanalized.
- Acute multiple cerebral infarction occurs in time, but no abnormality is found in the responsible vessels.

– Other cryptogenic

- Failure to meet the diagnostic criteria for cryptogenic cerebral embolism.

– Incomplete evaluation

- The examiner judges that the necessary inspection items are not completed.
- Unclassified

– There is more than one etiological evidence, which meets more than two (inclusive) or has no "highly probable" diagnostic criteria.

Appendix 3. Additional Safety Information

1. Life-threatening

"Life-threatening" means that if an AE occurs, the subject has a direct risk of death, or it was suspected that if the drug is used or continued to be used, the subject may die. "Life-threatening" does not mean that if AE occurs in a more serious form, it may cause death (such as controlled hepatitis without liver failure).

Hospitalization

Outpatient treatment in the emergency room itself is not a serious AE, but the reasons for outpatient treatment (such as bronchospasm and laryngeal edema) may be a serious AE. If the subject has a disease, before he / she is enrolled into the study, as long as the disease does not deteriorate in an unexpected manner during the process, the admission and / or surgery planned before or during the study is not considered as AE.

2. Important medical event or medical intervention

Important medical events may not be immediately life-threatening or cause death, hospitalization, disability or dysfunction, but may harm the subject or may require medical intervention to prevent the occurrence of one item or several items listed in the SAE definition. When determining whether a case is serious, medical and scientific judgment should be made. The above incident is usually considered serious.

Simply stopping the administration of the drug does not mean it is an important medical event; medical judgment must be made. Examples:

- Angioedema is not serious enough to require intubation, but requires intravenous hydrocortisone treatment.
- Hepatotoxicity caused by acetaminophen (paracetamol) requires N-acetylcysteine treatment.
- Intensive treatment of allergic bronchospasm in the emergency room or at home.
- Blood dyscrasia without hospitalization (such as neutropenia or anemia which require blood transfusion) or the emergence of
- Convulsions drug dependence or drug abuse

3. Guidelines for explaining cause-and-effect question

When determining the "reasonable possibilities" that an AE may be caused by a drug, the following factors should be considered.

- Time course. Exposure to suspected drugs. Has the subject been actually administered suspected drugs? Is there a reasonable sequential relationship between the occurrence of AE and the administration of suspected drugs?

- Consistency with known drug characteristics. Are the features of AE consistent with the pharmacology and toxicology of suspected drugs or drugs with the same pharmacological category? Is it possible to anticipate the appearance of AE from the pharmacological properties of suspected drugs?
- Dechallenge test. Does AE subside or relieve when the dose of suspected drugs is stopped or reduced?
- No alternative reason. AE cannot be reasonably explained through other etiology, such as underlying diseases, other drugs, other host or environmental factors.
- Rechallenge test. If suspected drugs are given again after AE disappear, does AE reoccur? Caution is required for testing in this way, and it is generally not recommended.
- Laboratory testing. A specific laboratory test (if carried out) has confirmed the above relation.

For an AE with one or more factors, it can be considered that there is a "reasonable possibility".

On the contrary, if all of the above criteria are not applicable, or there is no evidence of exposure and a reasonable time course, but any dechallenge (if carried out) results are negative or ambiguous, or there is another more probable reason for AE, It is considered that there is no "reasonable possibility" for causality. When encountering complex cases, other factors may be considered, such as:

- Is it a typical feature of overdose?
- Is there a known mechanism?

In addition to obtaining further evidence that can exclude "reasonable possibility" causality, the "reasonable possibility" causality in ambiguous cases should be taken into consideration. The deterioration of the disease due to lack of curative effect should be classified as no reasonable possibility.

Appendix 4. ASPECT Rating Scale

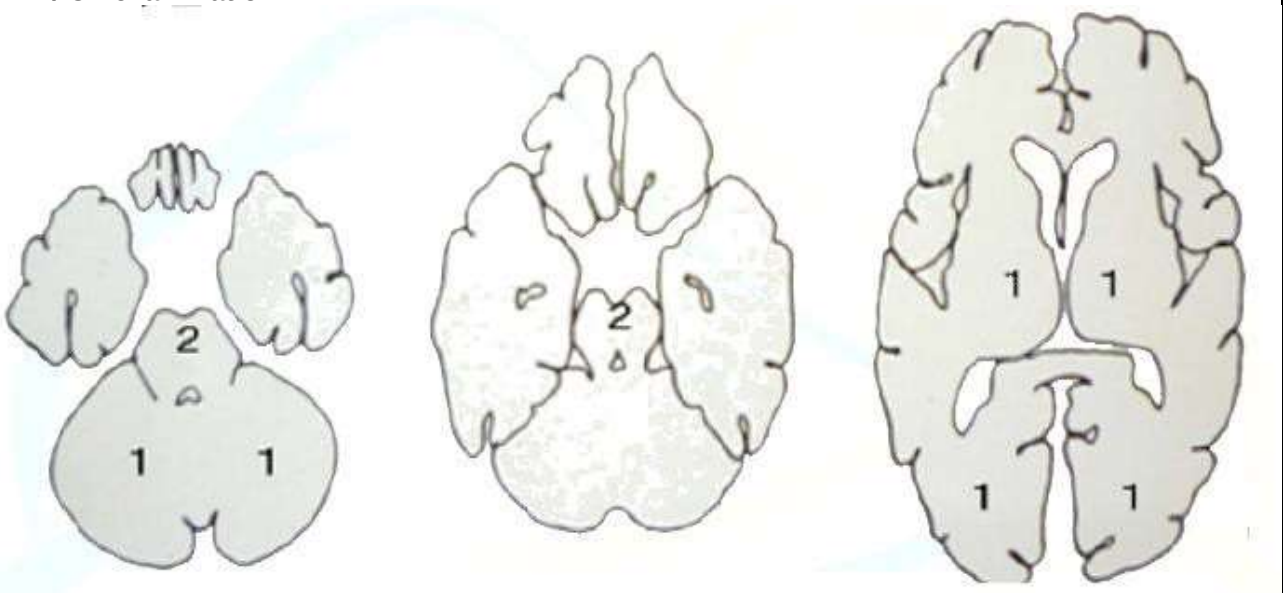
For patients with ischemic stroke, fill in the blank according to the sequence result of the most serious CT / MRI-DWI.

1. Anterior circulation ASPECT score (0 – 10): (see the table below ▼)	
Whether to evaluate:□$_1$ Yes□$_2$ No□$_3$ Not Evaluable□$_4$ Unknown If yes, the evaluation date is:|2|0|1|_|year|_|_|month|_|_|day	
MRI / CT examination:	
Subcortical Structures:	
(1) Caudate (C)	□$_1$
(2) Lentiform nucleus (L)	□$_2$
(3) Internal Capsule (IC)	□$_3$
MCA Cortex	
(4) Anterior MCA cortex (M1)	□$_4$
(5) Insular Ribbon (I)	□$_5$
(6) MCA cortex lateral to the insular ribbon (M2)	□$_6$
(7) Posterior MCA cortex (M3)	□$_7$
(8) Anterior cortex immediately rostal to M1 (M4)	□$_8$
(9) Lateral cortex immediately rostal to M3 (M5)	□$_9$
(10) Posterior cortex immediately rostal to M3 (M6)	□$_{10}$
The initial score is 10 points,and 1 point is deducted from the initial score for every region involved in early ischemic changes. **Anterior circulation ASPECTS score** = 10—Total score for all 10 regions is|_|_|points	

2. Posterior circulation ASPECT score (0 – 10): (see the table below ▼)

Whether to evaluate:□1 Yes□2 No□3 Not Evaluable□4 Unknown If yes, the evaluation date is:|2|0|1|_|year|_|_|month|_|_|day

MRI / CT examination:



Regions	Score
Thalamus	□1 0 point on the left □2 0 point on the right□3 Not evaluable
	□1 0 point on the right □2 1 point on the right □3 Not evaluable
Occipito-temporal region	□1 0 point on the left □2 0 point on the right□3 Not evaluable
	□1 0 point on the right □2 1 point on the right □3 Not evaluable
Any region of the midbrain	□1 0 point □2 2 points □3 Not evaluable
Any region of pons	□1 0 point □2 2 points □3 Not evaluable
Cerebellum	□1 0 point on the left □2 0 point on the right□3 Not evaluable
	□1 0 point on the right □2 1 point on the right □3 Not evaluable
The initial score is 10 points, and 1 point is deducted from the initial score for every region involved in early ischemic changes. **Anterior circulation ASPECTS score**=10－Total score for all 10 regions is |_|_| points	

Appendix 5. Modified Rankin Scale

Description of Patients	Score
No symptoms	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
Death	6

Guide to Performing the Rankin Scale Assessment

The Rankin Scale Assessment is used to measure the functional recovery of patients after stroke. The official definitions of each category are shown below in bold, and the italicised text provides guidance that may reduce inter-observer variability, without requiring a structured interview. Note that only symptoms arising since the stroke should be considered. Walking aids or other necessary mechanical devices apart from wheelchairs are disregarded provided that the patient can use these without external assistance.

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

0- No symptoms

The patient should be unaware of any new limitation of symptom caused by the stroke, however minor.

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

The patient has some symptoms as a result of the stroke, whether physical or cognitive – for example affecting speech, reading or writing; or physical movement; or sensation; or vision; or swallowing; or mood – but can continue to take part in all previous work, social and leisure activities. The crucial question to distinguish grade 1 from grade 2 (below) may be, 'is there anything that you can no longer do that you used to do until you had the stroke?' As a guide, an activity that was undertaken more frequently than monthly could be regarded as a 'usual activity'.

2- Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

The patient will be unable to undertake some activity that was possible before the stroke (e.g. driving a car, dancing, reading or working) but is still able to look after his/herself without help from others on a day to day basis. Thus, the patient can manage dressing, moving around, feeding, toileting, preparing simple meals, shopping, and travelling locally without needing assistance from anyone else. Supervision is not necessary. This grade assumes that the patient could be left alone at home for periods of a week or more without concern.

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

At this grade the patient is independently mobile (using a walking aid of frame if necessary) and can manage dressing, toileting, feeding, etc. but needs help from someone else for more complex tasks. For example, someone else may need to undertake shopping, cooking or cleaning and will need to visit the patient more often that weekly to ensure that these activities are completed. The assistance can be advisory rather than physical: for example, a patient who needs supervision or encouragement to cope with financial affairs would be in this grade.

4- Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

The patient requires someone else to help with some daily tasks, whether walking, dressing, toileting or eating. This patient will be visited at least once and usually twice or more times daily, or must live in proximity to a carer. To distinguish grade 4 from grade 5 (below), consider whether the patient can regularly be left alone for moderate periods during the day

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

Someone else will always need to be available during the day and at times during the night, though not necessarily a trained nurse.

6- Death

Appendix 6. National Institutes of Health Stroke Scale (NIHSS)

Administer stroke scale items in the order listed. Record 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).
If some items are not evaluated, they should be specified in the table.

	Tests	Score
1a	Level of consciousness The investigator must choose response, even 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 areflexic.
1b	Level of Consciousness (LOC) Questions The patient is asked the month and his/her age (It is important that only the initial answer be graded and that the examiner does not "help" the patient with cues). 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.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
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. Only the first attempt is scored. 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. Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands.	0 = Answers both questions correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2	Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1.	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.

	Tests	Score
	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.	
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).
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. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete (absence of facial movement in the upper and lower face).
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. The examiner can lift the patient's arms to the appropriate position and encourage the patient to persevere. Only assess the affected side.	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. Amputation or joint fusion, explain: _____
6	Motor Leg:	0 = No drift; leg holds 30-degree position for full 5 seconds.

	Tests	**Score**
	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. The examiner can lift the patient's arms to the appropriate position	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.

	and encourage the patient to persevere. Only assess the affected side.	4 = No movement. Amputation or joint fusion, explain:
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. In case of blindness, test by having the patient touch nose from extended arm position. Only in the case of amputation or joint fusion, the examiner should record the score as 9, and clearly write the explanation for this choice.	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs or above.
8	Sensory: Check with a needle. Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in patients with sensory deficits related to stroke 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.
9	Language: Naming, reading test. 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.	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. 2 = Severe aphasia; 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; examiner carries burden of communication.

	Tests	**Score**
	Patient with trachea cannula writes the answer with a pen Coma patient (1a = 3), 3 points, choose a score for the trance or non-cooperator, but 3 points are only for mute or people who do not follow instructions at all.	3 = Mute, global aphasia; no usable speech or auditory comprehension.
10	Dysarthria:	0 = Normal.

	Do not tell the patient why he or she is being tested. Patient will be asked 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 9, and clearly write an explanation for this choice.	1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Patient's speech is so slurred as to be unintelligible. 9 = Intubated or other physical barrier, explain:_
11	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. The doctor encourages the patient to look carefully at the picture and identify the features on the left and right sides of the picture. If the patient can not recognize part of the side picture, it is regarded as abnormal. Then, the doctor asked the patient to close his eyes and measure the sense of acupuncture on the arm or leg to check the bilateral skin sensation. If the patient feels neglected on one side, it is abnormal.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

Appendix 7. EuroQol-5 Dimensions (EQ-5D)

Under each heading, please tick the ONE box that best describes your health TODAY	
MOBILITY	□1 I have no problems in walking about □2 I have some problems in walking about □3 I am confined to bed
Self-care	□1 I have no problems with self-care □2 I have some problems washing or dressing myself □3 I am unable to wash or dress myself
Usual Activities (e.g., work, study, housework, family or leisure activities)	□1 I have no problems with performing my usual activities □2 I have some problems with performing my usual activities □3 I am unable to perform my usual activities
Pain/Discomfort	□1 I have no pain or discomfort □2 I have moderate pain or discomfort □3 I have extreme pain or discomfort
Anxiety/Depression	□1 I am not anxious or depressed □2 I am moderately anxious or depressed □3 I am extremely anxious or depressed