Statistical Analysis Plan(SAP)

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Direct Intra-arterial thrombectomy in order to Revascularize AIS patients with large vessel occlusion Efficiently in Chinese Tertiary hospitals: a Multicenter randomized clinical Trial (DIRECT-MT)

Study Statistician (CRO):

Sam Zhong

Shanghai KNOWLANDS MedPharm Consulting Co., Ltd.

Sponsor:

Changhai Hospital Affiliated to the Second Military Medical University

SIGNATURE PAGE

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Sam Zhong — Date

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Sponsor

Pengfei Yang

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2019.10.22

Date

Revision history

Version	Date	Revision description
1.0	30-Nov-2018	Initial version, not applicable
2.0	21-Oct-2019	1. The SAP was revised to this current version primarily considering the protocol has been updated to version 3.0 (20-Aug-2019) from version 2.0 (31-Aug-2018). 2. In the current SAP, the primary analysis population was renamed to intention-to-treat population (ITT) instead of the full analysis set, while the same definition remained. And also elaborated several basic criteria for subjects entering PPS, see chapter 2.2. 3. Following the original statistical methodology strictly, this current SAP provided more wording details regarding statistical analysis variables and statistical methods, which involved demographic characteristics, efficacy, the definitive rules of subgroups, safety and analysis of quality of life as well, see chapter 2. 4. The current SAP added some subgroup analyses for primary efficacy endpoint, see chapter 2.3 for details. 5. A few document styles and formats in the current SAP template were adjusted as appropriate.

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LIST OF ABBREVIATIONS

Abbreviations	Definitions
AComA	Anterior communicating artery
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Events of Special Interest
AIS	Acute Ischemic Stroke
AOL	Arterial occlusive lesion classification
APTT	Activated Partial Thromboplastin Time
ASPECTS	the Alberta Stroke Program Early CT Score
BI	Barthel Index
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
cOR	Common odds ratio
CT	Computed tomography
CTA	Computed tomography angiography
CRF	Case Report Form
CRO	Contract Research Organization
DSA	Digital substraction angiography
DSMB	Data Safety Monitoring Board
EC	Ethics committee
eTICI	extended treatment in cerebral ischemia scale
EQ5D-5L	EuroQol-5 dimensions-5 level
EVT	Endovascular treatment
IAT	Intra-arterial treatment
INR	International normalized ratio
ITT	Intention-to-treat
IVT	Intravenous treatment
LOC	Level of consciousness
mAOL	Modified arterial occlusive lesion classification
MCA	Middle cerebral artery

Abbreviations	Definitions
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
MT	Mechanical thrombectomy
NCCT	Non-contrast computed tomography
NIHSS	National Institute of Health stroke scale
PPS	Per-protocol set
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
sICH	Symptomatic intracerebral hemorrhage
SOC	System organ class

1 STUDY OVERVIEW

This Statistical Analysis Plan (SAP) is developed based on the most recent study protocol (Version 3.0, 20-Aug-2019) and Case Report Form (CRF, Version 1.4, 13-Nov-2018), and details the statistical analysis strategies and methods for the study.

This SAP predefines the statistical analysis population, variables and analysis methods before database lock to ensure the reliability of the study results.

1.1 STUDY DESIGN AND RANDOMIZATION

This is a multicenter prospective randomized clinical trial with open-label treatment and blinded outcome assessment (PROBE). The study will run for 4 years in intervention centers. Randomization will be stratified by center. The treatment allocation is 1:1 for:

- Direct IAT (MT),
- IVT followed by IAT (IVT plus MT)

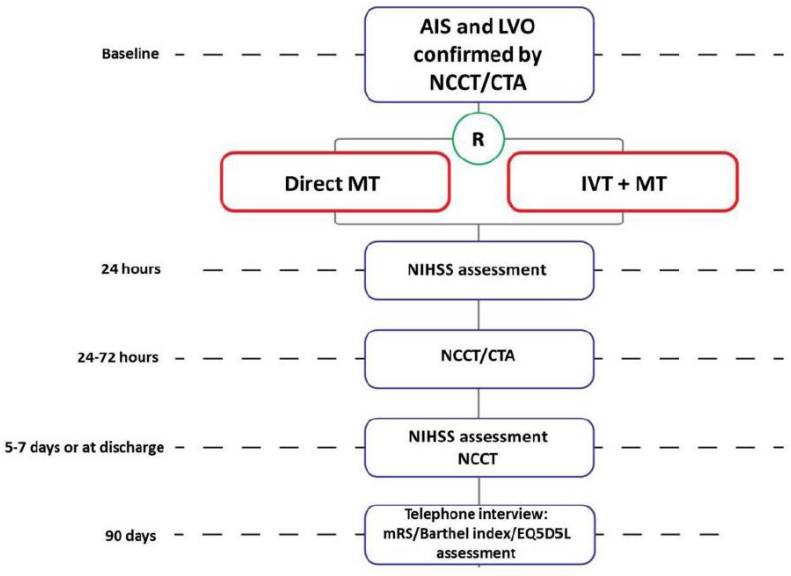

Figure 1 Patient flow in the trial

The intervention group will undergo immediate intra-arterial treatment (IAT) using a stent retriever, as recommended by the steering committee. Patients in the control group will receive alteplase intravenous treatment (IVT) (0.9 mg/kg with a maximum dose of 90 mg), followed by IAT using a stent retriever.

Local application (intra-arterial) of alteplase is allowed in any of the patients included in the DIRECT-MT if necessary. Patients pre-treated with IVT should not receive more than 30mg alteplase during intra-arterial treatment. Delivery of alteplase in shots of 5 mg in 5-10 minutes intervals is recommended. An equivalent dose of 400,000 U urokinase, delivered in shots of 50.000 - 100.000 U, in 5-10 minutes time intervals, is also accepted as escape medication in individual cases. If successful reperfusion (eTICI 2b-3) is not achieved in the direct MT group, IVT with 0.9 mg/kg may be initiated if the 4.5 hour window or maximum dose is not exceeded.

1.2 STUDY OBJECTIVES

The primary objective of this trial is to assess the effect of direct IAT compared with IVT followed by IAT, on functional outcome in patients with acute ischemic stroke (AIS), caused by an anterior circulation occlusion that is confirmed by Computed tomography angiography (CTA).

The secondary objective is to explore for superiority of direct IAT relative to IVT followed by IAT.

The tertiary objective is to assess the effect of direct IAT compared with IVT with IAT on neurological recovery (NIHSS), infarct size and occurrence of Symptomatic intracerebral hemorrhage (sICH).

The fourth objective is to collect thrombi and to analyze them with respect to their potential for treatment effect modification.

1.3 STUDY OUTCOMES

Primary outcome:

The primary outcome is the score on the modified Rankin Scale (mRS) (Table 1 in Appendix) at 90 days (±14 days). The mRS is the preferred disability parameter for clinical trials in stroke. The mRS is an ordinal hierarchical scale incorporating six categories from 0 up to and including 5, and describes the range of disability encountered post stroke. "Death" is assigned a score of 6. Assessment of outcome on the mRS will be performed by outcome committee, blinded to the allocated and actually received treatment. Their assessment will be based on standardized reports of a telephone interview by trained research personnel who are not aware of treatment allocation.

Secondary outcomes:

- Death within 90 days (±14 days)

- Pre-interventional recanalization
- extended treatment in cerebral ischemia scale (eTICI) score on final angiography of IAT (Table 2 in Appendix)
- Recanalization rate at 24-72 hours, assessed with CTA
- Score on the NIHSS at 24±6 hours and 5 -7 days. (Table 3 in Appendix)
- Final infarct volume at 5-7 days. Final infarct volume will be assessed with the use of an automated, validated algorithm. Infarct size at day 5-7 will be compared with plain computed tomography (CT) and perfusion CT results (if available) at baseline.
- Dichotomized mRS of 0-1 vs. 2-6 at 90 days (±14 days)
- Dichotomized mRS of 0-2 vs. 3-6 at 90 days (±14 days)
- Dichotomized mRS of 0-3 vs. 4-6 at 90 days (±14 days)
- Score on the EuroQol-5 dimensions-5 level (EQ5D-5L) (Table 4 in Appendix) and Barthel index (BI) (Table 5 in Appendix) at 90 days (±14 days)

Safety outcomes:

- Hemorrhages according to the Heidelberg criteria [1]
- sICH scored according to the Heidelberg criteria [2]
- Embolization in new territory on angiography during IAT
- Occurrence of aneurysma spurium
- Occurrence of groin hematoma
- Infarction in new territory at 5-7 days (Table 6 in Appendix)
- Death from all causes within 90 days (±14 days)

1.4 SAMPLE SIZE CALCULATION

We based our estimations on the distribution of the mRS in the control group of the trial, which we derived from the intervention group of the MR CLEAN trial [3]: mRS 0: 3%; mRS 1: 9%; mRS 2: 21%; mRS 3: 18%; mRS 4: 22%; mRS 5: 6% and mRS 6: 21%. We assumed a favorable treatment effect with a common odds ratio (cOR) of 1.163, corresponding to a 4% absolute increase in the rate of mRS scores of 0-2. The main purpose is to demonstrate non-inferiority, that is, the lower limit of the two-side 95% confidence interval does not cross the pre-specified cOR non-inferiority Cutoff of 0.8. In a simulation with 5000 runs we computed the proportion of positive trials, for a given sample size. A sample size of 710 was determined to detect the pre-defined non-

inferiority with a power of 80% and two-sided alpha of 0.05. Using covariate adjustment with at most 25%, a conservative 15% sample size reduction can be achieved, plus 5% dropout rate, leading to a final sample size of 636, 318 per arm.

1.5 STUDY PROCEDURES

Before starting the study, patients or their guardians must read and sign the informed consent approved by the current Ethics Committee (EC). All research steps should be carried out within the time window specified in the study protocol.

All patients will undergo assessment of the NIHSS at baseline, 24±6 hours and 5-7 days, which is routine in clinical procedure. It will be carried out by certified assessors. Patients will undergo NCCT and CTA at baseline. After 24-72 hours, CTA is repeated to determine recanalization. At 5-7 days, patients will undergo non-contrast computed tomography (NCCT) to assess infarct size.

In addition, this trial also makes use of "waste material": retrieved thrombi during intervention. These thrombi will be stored in the participating study centers for follow-up analysis.

1.5.1 Procedures

All the procedures to be recorded are listed in Table 1.

Table 1 Procedures

Items	Procedures(includes but not limited to:)
Demography	Date of birth (based on valid identity documents), sex, age
Medical History	Disease history, smoking/alcohol drinking history, medications
Modified Rankin Scale	Disability level, ranging from 0~5
Glasgow coma Scale	Eye Opening, Best Verbal Response, Best Motor Response
Vital Signs	Systolic/diastolic blood pressure, heart rate, body temperature, height, weight
NIHSS	Level of consciousness (LOC), LOC Questions, LOC Commands, Best Gaze, Visual, Facial palsy, Motor arm, Motor leg, Limb ataxia, Sensory, Best language, Dysarthria, Extinction and Inattention
Laboratory tests	Serum glucose, Activated Partial Thromboplastin Time (APTT), International normalized ratio (INR), Thrombocyte count, Serum creatinine
eTICI	eTICI classification includes 0, 1, 2a, 2b, 2C and 3
EQ5D-5L score	Mobility, Self-Care, Usual-Activities, Pain/Discomfort, Anxiety/Depression
BARTHEL index	Feeding, Bathing, Grooming, dressing, Bowels, Bladder, Toilet use, Transfers(bed to chair and back), Mobility(on level surfaces), Stairs
Neuroimaging	CT, CTA, MRI and other imaging examinations

2 STATISTICAL METHODOLOGY

2.1 STATISTICAL VARIABLES

2.1.1 Background and demographic characteristics

The demographic and baseline information will include age, sex, medical history, smoking history and medications used at home.

2.1.2 Efficacy

2.1.2.1 Primary efficacy variables

Primary efficacy outcome is mRS score change at 90 days (±14 days) , which will be blindly evaluated by an independent Outcome Assessment Committee.

The mRS is the preferred disability parameter for clinical trials in stroke. The mRS is an ordinal hierarchical scale incorporating six categories from 0 up to and including 5, and describes the range of disability encountered post stroke. "Death" is assigned a score of 6 (Table 1 in Appendix).

2.1.2.2 Secondary efficacy variables

- Death within 90 days (±14 days)
- Pre-interventional recanalization
- eTICI score on final angiography of IAT. (Table 2 in Appendix)
- Recanalization rate at 24-72 hours, assessed with CTA
- Score on the NIHSS at 24±6 hours and 5 -7 days. (Table 3 in Appendix)
- Final infarct volume at 5-7 days. Final infarct volume will be assessed with the use of an automated, validated algorithm. Infarct size at day 5-7 will be compared with plain CT and perfusion CT results (if available) at baseline.
- Dichotomized mRS of 0-1 vs. 2-6 at 90 days (±14 days)
- Dichotomized mRS of 0-2 vs. 3-6 at 90 days (±14 days)
- Dichotomized mRS of 0-3 vs. 4-6 at 90 days (±14 days)
- Dichotomized mRS of 0-4 vs. 5-6 at 90 days (±14 days)
- Dichotomized mRS of 0-5 vs. 6 at 90 days (±14 days)

- Score on the EQ5D-5L and Barthel index at 90 days (±14 days)

Pre-interventional recanalization： Recanalization rate (eTICI 2b, 2c or 3) before patients received mechanical intra-arterial treatment according to the DSA.

Recanalization rate at 24-72 hours: defined as the proportion of patients in whom recanalization as determined on 24-72 hours CTA is achieved.

eTICI score: eTICI assessment will be performed post IAT. The eTICI classification includes 0, 1, 2a, 2b, 2c and 3 (Table 2 in Appendix).

NIHSS score: The NIHSS is an ordinal hierarchical scale to evaluate the severity of stroke by assessing a patient's performance. Scores range from 0 to 42, with higher scores indicating a more severe deficit (Table 3 in Appendix). NIHSS assessment will be performed at baseline, 24±6 hours post operation and 5-7 days post operation.

The EuroQoL 5-dimensions 5-level (EQ-5D-5L) questionnaire is a standardized measure of health outcome that has been used extensively in patients with stroke (Table 5 in Appendix). EQ5D-5L assessment will be performed at 90±14 days post operation.

The Barthel index (BI) is an ordinal scale used to measure performance in 10 activities of daily living (ADL). Test scores range from 0 to 100, with higher scores indicating better performance in these daily activities (Table 4 in Appendix). BI assessment will be performed at 90±14 days post operation.

2.1.3 Safety

2.1.3.1 Adverse events (AEs)

This study focused on the serious adverse events (SAEs) and Adverse Events of Special Interest (AESIs), and all reported SAEs will be blindly reviewed by an independent Adverse Event Committee.

All SAEs and AESIs will be coded using MedDRA 22.0 or higher, before database lock. MedDRA System Organ Class (SOC) and Preferred Term (PT) will be summarized.

Classification of serious adverse events

All SAEs will be classified as follows,

- Death
- Symptomatic intracranial hemorrhage
- De novo Ischemic Stroke
- Large or malignant middle cerebral artery (MCA) infarction

- Pneumonia (Aspiration and others)
- Contrast allergic reaction
- Major bleeding due to femoral artery access complications including groin hematoma, retroperitoneal hematoma
- Acute kidney injury
- Others

Adverse Events of Special Interest
Adverse events of special interest for this study include aspiration pneumonia and allergic contrast reactions.

2.1.3.2 Laboratory variables

Baseline laboratory tests will be conducted at screening visit, which include blood glucose (mmol/L), prothrombin time (sec), international standardized ratio, platelet count (*10^9), serum creatinine (umol/L).

2.1.3.3 Vital signs

At screening visit, the following vital signs will be measured: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beat/min), body temperature (℃), height (cm), weight (kg).

2.1.3.4 Neuroimaging

CT and CTA will be performed at baseline and follow-up visit and the findings of which will be blindly evaluated blindly by an independent Imaging Committee (Core lab), including hyperdense, the Alberta Stroke Program Early CT Score (ASPECTS), another occlusion location of anterior circulation except target lesion, anterior communicating artery (AComA), intracranial hemorrhages (Table 7 in Appendix), midline shift present, target vessel stent placement, modified arterial occlusive lesion classification (mAOL, (Table 8 in Appendix)), vascular occlusion, etc.

The newly affected territory of the middle cerebral artery was graded by the systematic quantitative scoring system, e.g. ASPECTS. It will be performed at baseline visit and follow-up visit. ASPECTS is allotted 10 points, including caudate, lentiform, internal capsule, insular cortex, M1, M2, M3, M4, M5, M6. One point is subtracted for an area of early ischaemic change, such as focal swelling, or parenchymal hypoattenuation, for each of the defined regions. A score of 0 indicates diffuse ischaemia throughout the territory of the middle cerebral artery.

2.1.4 Health economics

None.

2.2 STATISTICAL ANALYSIS POPULATION

The analysis populations include intention-to-treat population (ITT) and per-protocol set (PPS) for this study.

2.2.1 Intention-to-treat population

All subjects who were randomized will be included in the intention-to-treat population (ITT) according to intention-to-treat principles, in which subjects will be analyzed according to the group assigned by randomization. ITT is the primary efficacy analysis set for this study.

2.2.2 Per-protocol set

Per-protocol set (PPS) is a subset of ITT, including all randomized subjects who have been treated in the study without major protocol deviations that may significantly impact the interpretation of efficacy results. Detailed protocol deviation criteria will be determined at the latest before database lock. PPS will be used for the primary efficacy outcome and safety analysis. Subjects entering PPS need to satisfy all the following basic criteria:

(1) Meet all the eligibility criteria specified in the study protocol;

(2) The subjects were randomized and received the assigned treatment, i.e.

- No IVT was administered before the intended endovascular treatment (EVT) in the intervention group (direct IAT group);
- IVT was administered before the intended EVT in patients in the control group.

(3) Underwent groin puncture, with exception of patients with clinical recovery precluding EVT (due to presumed recanalization before mechanical thrombectomy).

2.2.3 Subject disposition

The number and proportion of screened, randomized, treated and analyzed subjects will be provided. Where necessary, the CONSORT flow chart will be presented to describe the subject disposition in the statistical analysis report.

2.3 STATISTICAL METHODS

For normally distributed continuous data, the following statistics will be provided: number, mean, standard deviation (SD), minimum and maximum. For non-normally distributed continuous data, number, median, lower quartile (Q1), upper quartile (Q3) will be provided, unless otherwise stated. Categorical data will be summarized in terms of the number of patients and percentages.

For summary statistics, mean, standard deviation, median and quartiles will be reported to 1 more decimal place than the original data, while the 95% confidence interval (CI) will be reported to 2. Minimum and maximum values will be reported to the same number of significant digits as the original data. In the frequency table, the percentages will keep 1 decimal, the p values keep 4 decimal or displayed as "<0.0001".

2.3.1 Demography and baseline characteristics

Demography and baseline characteristics will be statistically summarized by treatment group.

In addition, the medical history, smoking history, drug treatment history and other information will be summarized. Data listings will be provided where necessary.

2.3.2 Analysis of efficacy outcomes

All efficacy data analyses will be based on ITT and for primary endpoint PPS will also be used.

2.3.2.1 Primary efficacy outcome

The primary effect parameter is the common odds ratio, which will be estimated by ordinal logistic regression (proportional odds model), which represent the shift on the full distribution of the modified Rankin Scale at 90±14 days. Estimations will be adjusted by known prognostic variables such as age (median), pre-stroke mRS (continuous), time from symptom onset to randomization ("<=Q1", ">Q1, <=Q2", ">Q2, <=Q3", ">Q3"), stroke severity (NIHSS, median) and collaterals (Grade 0-1, Grade 2-3). Adjusted and unadjusted estimations and their corresponding 95% confidence intervals will be reported. To assess non-inferiority of direct MT compared to IVT with MT, we will assess whether the 95% CI lower bound of the adjusted common odds ratio cross our pre-specified non-inferiority boundary (0.8).

The following SAS procedure will be used for ordered logistic regression analysis (proportional odds model):

```
Proc  logistic data=XXX;
Class TRT FactorA …;
Model mRS90= TRT AGE FactorA …;
```

```
Run;
```

2.3.2.2 Secondary efficacy outcome

Continuous secondary efficacy outcomes are mainly infarct size at 5-7 days after operation and recanalization rate before intervention as well. Analysis for these outcomes will be mainly based on statistical descriptions. Where necessary, analysis of variance or corresponding non-parametric test will be used for between-group comparisons. If applicable, the linear regression analysis will be used with adjustment for the same covariate variables as the primary outcome analysis. When deemed necessary, log or other common transformation of non-normal distribution will be used.

Categorical secondary outcomes include mortality at 90 days after operation, recanalization rate at 24-72 hours, dichotomized mRS score at 90 days after operation (0-1 vs. 2-6, 0-2 vs. 3-6, 0-3 vs. 4-6), successful recanalization before and after Mechanical thrombectomy (MT), and eTICI score at MT final angiography. Chi-square test will be used for comparison between the two groups, or Fisher's exact test will be used for comparison when applicable. The categorical secondary outcomes will be analyzed by logistic or ordered regression analysis to provide a common odds ratio and its confidence interval, if applicable. The adjustment method is the same as that in the primary outcome analysis.

2.3.2.3 Subgroup analysis

Pre-specified subgroup analysis will be performed by examining the interaction between specific baseline characteristics and treatment. Baseline grouping factors for subgroup analysis include, but are not limited to:

- Age
- Baseline NIHSS
- Quartiles of time from onset of symptoms to randomization
- Quartiles of time from onset of symptoms to groin puncture
- Quartiles of time from randomization to groin puncture
- Quartiles of time from onset of symptoms to revascularization
- Quartiles of time from randomization to revascularization
- Ipsilateral extracranial carotid tandem lesion
- Occlusion location
- Collaterals (Table 9 in Appendix)

- Large vessel occlusion due to different etiologies
- Thrombus perviousness
- Thrombus density

See the detailed description of subgroup types and definitions in Appendix Table 10.

2.3.2.4 Multiplicity

This study does not consider multiplicity issues and therefore does not adjust significance levels based on multiplicity tests, unless specified otherwise.

2.3.3 Study treatment

2.3.3.1 Intravenous alteplase therapy

Intravenous alteplase therapy will be summarized (only applied to IVT plus MT group), including whether IVT is performed, planned alteplase dose (mg) and residual alteplase volume (ml).

2.3.3.2 Intra-arterial treatment

A descriptive summary of intra-arterial therapy will be provided according to the treatment groups, including anesthesia management, pre-treatment, treatment, eTICI score as determined by final angiography, thrombectomy, intra-operative non-study drugs, stent implantation/balloon dilatation at the intracranial atherosclerosis occlusion site.

2.3.3.3 Digital substraction angiography (DSA)

The results of DSA will be blindly evaluated by the independent Imaging Committee (Core lab) , including but not limited to: ipsilateral extracranial carotid tandem lesion, intracranial arterial occlusions, another occlusion location of anterior circulation except target lesion, arterial occlusive lesion classification (AOL) and intracranial atherosclerosis occlusion, will be summarized according to the treatment groups.

2.3.4 Safety analysis

In this study, the safety analysis will be mainly based on statistical description. All the analyses will be based on PPS.

2.3.4.1 Analysis of adverse events (AEs)

The number and percentage of subjects who had at least one serious adverse event, classification of serious adverse event, adverse events of special interest and classification of adverse events of special interest from study will be provided.

- All SAEs will be summarized by SOC and PT;

- All AESIs will be summarized by SOC and PT;

2.3.4.2 Clinical laboratory data analysis

Laboratory tests included blood sugar, prothrombin time, international standardized ratio, platelet count and serum creatinine.

For continuous laboratory parameters, summary statistics, including number of subjects, mean, standard deviation, median, minimum and maximum will be provided for observed values for each parameter.

If a lab test result is recorded as "<10", then it will be summarized as a value of "5", if applicable; and likewise, ">10" will be summarized as "10".

2.3.4.3 Analysis of vital signs

Summaries of vital signs parameters will be presented by treatment group, using summary statistics, including number of subjects, mean, standard deviation, median, minimum and maximum for observed values for each parameter.

2.3.4.4 Analysis of neuroimaging

ASPECTS (0-10) and change from baseline are continuous variables and will be presented with summary statistics. The frequency table of each point will also be provided by treatment groups.

Other results of CT and CTA will be summarized using frequency table by treatment groups (if necessary).

2.3.5 Analysis of quality of life

2.3.5.1 NIHSS score

NIHSS (0-42) score and change from baseline are continuous variables and will be presented with summary statistics, including number of subjects, mean, standard deviation, median, minimum and maximum, by treatment groups and by visits. Repeated measures of variance analysis will be used to explore the impact of treatment grouping visits and NIHSS baseline levels.

2.3.5.2 EQ5D-5L score

The frequency and percentage of EQ5D-5L scale will be summarized according to each dimension. If necessary, Chi-square test will be used for comparison between the two groups, or Fisher's exact test will be used for comparison when applicable.

2.3.5.3 Barthel index

Barthel score is a continuous variable (0-100) and will be summarized using number, mean, standard deviation, median, minimum and maximum, by treatment groups. The frequency table of each class level will also be provided.

2.4 DATA PROCESSING CONVENTIONS

2.4.1 Definition of baseline

In this study, baseline values are defined as those data collected before intervention (screening visit). When multiple data collections occur during the baseline period, the final data shall prevail in principle, unless explicitly stated.

2.4.2 Missing data

We will report proportions of missing values for all collected variables where needed.

Baseline characteristics missing data will be imputed by regression interpolation as appropriate.

If there is a large number of missing data on efficacy and safety, an evaluation on the missing data should be conducted before analysis, and will propose and determine the solution before database lock.

For patients who died within the study period, the worst scores will be assigned for all not-assessed clinical outcome measures in their analyses, as follows Table 2.

Table 2 The worst scores of clinical outcomes

Clinical outcomes	The worst scores
mRS	6
NIHSS	42
The Barthel index	0

2.4.3 Time window

Not applicable.

2.4.4 Unscheduled visits

Not applicable.

2.4.5 Centers pooling

Unless specifically specified, this study will not consider the center effect, so it will not pool and analyze the data of each study center.

3 CHANGES TO PLANNED ANALYSES FROM THE PROTOCOL

Protocol version (Date)	Major Changes to Planned Analyses from the Protocol
Version 2.0 (31-Aug-2018)	● Recalculated the sample size according to the modified good outcome (Section 4.5 of the protocol) After revision: *We assumed a favorable treatment effect with a common odds ratio (cOR) of 1.163, corresponding to a 4% absolute increase in the rate of mRS scores of 0-2. The main aim of the trial is to demonstrate non-inferiority. To do so, the lower limit of the two-sided 95% confidence interval of the cOR should not cross the pre-specified non-inferiority boundary of 0.8.* *In a Monte Carlo simulation with 5000 runs we computed the proportion of positive trials, for a given sample size. A sample size of 710 was determined to detect the pre-defined non-inferiority with a power of 80% and two-sided alpha of 0.05. Using covariate adjustment with at most 25%, a conservative 15% sample size reduction can be achieved, plus 5% dropout rate, leading to a final sample size of 636, 318 per arm.* Before revision: *We based our estimations on the distribution of the modified Rankin Scale (mRS) in the control group of the trial, which we derived from the intervention group of the MR CLEAN trial (9): mRS 0: 3%; mRS 1: 9%; mRS 2: 21%; mRS 3: 18%; mRS 4: 22%; mRS 5: 6% and mRS 6: 21%. We assumed a favorable treatment effect with a common odds ratio (cOR) of 1.54, which corresponds to an absolute risk difference of having a score on the modified Rankin Scale of 0-2 of approximately 8%. The main purpose is to demonstrate non-inferiority, that is, the lower limit of the 95% confidence interval does not cross the pre-specified cOR non-inferiority Cutoff of 0.8. In a simulation with 5000 runs we computed the proportion of positive trials, for a given sample size. This yielded a sample size of 680, providing 99% power to detect a true treatment effect, with two-sided alpha =0.05. In the analysis we will use covariate adjustment, which reduces the required sample size with 25% (28, 29).*

	Therefore, the aim is to include 540 patients, 270 in each group of the trial, considering a dropout rate of 5%. ● Revised the interim analyses plan (Section 9.4 of the protocol) After revision: *DSMB plans to conduct two interim analyses to evaluate the treatment effect and the incidence of adverse reactions according to the procedure at the end of the 90-day follow-up of 1/3 and 2/3 subjects, respectively.* Before revision: *The DSMB will meet frequently, at least annually or after inclusion of the next 100 patients (whichever comes first) and assess the occurrence of adverse events by center and by procedure.* ● Modified Study committees member list Data Safety Monitoring Board, Outcome Assessment Committee and Adverse Event Adjudication Committee added.
Version 3.0 (20-Aug-2019)	● Subgroup analysis (Section 10.2 of the protocol) One subgroup added: *Large vessel occlusion due to different etiologies* ● Modified Study committees member list Imaging Assessment Committee added.

4 INTERIM ANALYSIS

A formal interim analysis is planned.

In order to increase the safety of the intervention, the trial will be monitored by an independent Data Safety Monitoring Board (DSMB). The DSMB will be chaired by a neurologist, and include a neuro-interventionist and an independent methodologist/ statistician. The DSMB plans to conduct two interim analyses to evaluate the treatment effect and the incidence of adverse reactions according to the procedure at the end of the 90-day follow-up of 1/3 and 2/3 subjects, respectively. During the period of patient enrollment into the study, interim analyses of mortality and of any other information that is available on major outcomes (including serious adverse events believed to be due to treatment) will be supplied, in strict confidence, to the chairman of the DSMB, along with any other analyses that the DSMB may request. In the light of these analyses, DSMB will advise the chairman of the Steering Committee if, in their view, the randomized comparisons in DIRECT-MT have provided both (i) "proof beyond reasonable doubt" that for all, or for some specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in outcome, and (ii) evidence that might reasonably be expected to materially influence patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a major outcome may be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the number of interim analyses is of little importance.

The advice(s) of the DSMB will be sent to the sponsor of the study by the chair of the steering committee. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the EC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

5 STATISTICAL ANALYSIS SOFTWARE

All statistical analysis and summary will be carried out using SAS 9.2 or higher version in this study. Software R 3.3.1 or higher version will be used for drawing plots if applicable.

6 REFERENCES

[1] Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Md State Med J. 1965;14:61-5.

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[3] Berkhemer OA, Fransen PS, Beumer D, van den BergL.A, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015372(1): 11-20

7 APPENDIX

Appendix table 1 Modified Rankin Scale

The modified Rankin Scale (mRS) is an ordinal hierarchical scale ranging from 0 to 5, with higher scores indicating more severe disability. A score of 6 has been added to signify death.

Category	Short description	Long description
0	No symptoms	No symptoms
1	Symptoms, no disability	Minor symptoms that do not interfere with lifestyle
2	Slight disability	Slight disability, symptoms that lead to some restriction in lifestyle, but do not interfere with the patient's capacity to look after himself.
3	Moderate disability	Moderate disability, symptoms that significantly restrict lifestyle and prevent totally independent existence
4	Moderately severe disability	Moderately severe disability, symptoms that clearly prevent independent existence though not needing constant attention
5	Severe disability	Severe disability, totally dependent patient requiring constant attention day and night.
6	Death	Death

Appendix table 2 Extended Treatment In Cerebral Ischemia (eTICI) Scale

eTICI grade	Short description	Long description
0	No perfusion	No antegrade flow beyond the point of occlusion
1	Limited reperfusion	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
2a	<50% reperfusion	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (eg, in 1 major division of the MCA and its territory)
2b	≥50% and <90% reperfusion	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (eg, in 2 major divisions of the MCA and its territories)
2c	≥90% reperfusion	Near complete antegrade reperfusion of the previously occluded target artery ischemic territory, except for slow flow or distal emboli in a few distal cortical vessels
3	100% reperfusion	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

Appendix table 3 NIH Stroke Scale

The NIHSS is an ordinal hierarchical scale to evaluate the severity of stroke by assessing a patient's performance. (23) Scores range from 0 to 42, with higher scores indicating a more severe deficit. 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).

Instructions	Scale definition
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; required 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. LOC Questions: The patient is asked the month and his/her age. The answer must be correct – there is not partial credit for being close. Phasic 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 examiners not "help" the patient with verbal or non-verbal clues.	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 hand 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 a 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, preexisting blindness, or other disorder of	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.

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 finger 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 in this case. If there is extinction, the 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 response 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 paralysis (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).
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.
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	0= Absent. 1= Present in one limb. 2= Present in two limbs.

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.	UN = Amputation or joint fusion: explain:
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; patients 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. 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 conservation 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.
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 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 by 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.
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	0= No abnormality. 1= Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory

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.	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 table 4 EUROQOL 5D-5L

The EuroQoL 5-dimensions 5-level (EQ-5D-5L) questionnaire is a standardized measure of health outcome that has been used extensively in patients with stroke.

Under each heading, please tick the ONE box that best describes your health TODAY.

Mobility

I have no problems in walking about
I have slight problems in walking about
I have moderate problems in walking about
I have severe problems in walking about
I am unable to walk about

Self-care

I have no problems washing or dressing myself
I have slight problems washing or dressing myself
I have moderate problems washing or dressing myself
I have severe problems washing or dressing myself
I am unable to wash or dress myself

Usual activities (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities
I have slight problems doing my usual activities
I have moderate problems doing my usual activities
I have severe problems doing my usual activities
I am unable to do my usual activities

Pain/discomfort

I have no pain or discomfort
I have slight pain or discomfort
I have moderate pain or discomfort
I have severe pain or discomfort
I have extreme pain or discomfort

Anxiety/depression

I am not anxious or depressed
I am slightly anxious or depressed
I am moderately anxious or depressed
I am severely anxious or depressed
I am extremely anxious or depressed

Appendix table 5 Barthel Index

The Barthel index (BI) is an ordinal scale used to measure performance in 10 activities of daily living (ADL). Test scores range from 0 to 100, with higher scores indicating better performance in these activities.

Category	Scale definition
Feeding	0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent
Bathing	0 = dependent 5 = independent (or in shower)
Grooming	0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)
Dressing	0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)
Bowels	0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent
Bladder	0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent
Toilet use	0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)
Transfers (bed to chair and back)	0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent
Mobility (on level surfaces)	0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards
Stairs	0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent

Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.

2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.

3. The need for supervision renders the patient not independent.

4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However, direct testing is not needed.

5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.

6. Middle categories imply that the patient supplies over 50 per cent of the effort.

7. Use of aids to be independent is allowed.

Appendix table 6 Classification of Infarct in a New Territory

Classification based on size		Classification based on catheter manipulation across territory ostium
Type I	≤2 mm diffusion lesion (unidentifiable on NCCT)	Type A Catheter was manipulated past the ostium of the new territory (e.g. large ACA infarct in a patient with an initial M1 occlusion): greater likelihood that infarct is related to the procedure Type B Catheter was not manipulated past the ostium of the new territory (e.g. left PICA infarct in a patient with an initial right M1 occlusion): lower likelihood that infarct is related to procedure
Type II	>2 mm to ≤ 20 mm lesion (potentially difficult to identify on CT scan)	
Type III	Large (> 20 mm) infarct	

Appendix table 7 Description of Intracranial Hemorrhages

Class	Type	Description
1 Hemorrhagic transformation of infarcted brain tissue		
1a	HI1	Scattered small petechiae, no mass effect
1b	HI2	Confluent petechiae, no mass effect
1c	PH1	Hematoma within infarcted tissue, occupying <30%, no substantive mass effect
2 Intracerebral hemorrhage within and beyond infarcted brain tissue		
	PH2	Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect
3 Intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage		
3a	rPH	Parenchymal hematoma remote from infarcted brain tissue
3b	IVH	Intraventricular hemorrhage
3c	SAH	Subarachnoid hemorrhage
3d	SDH	Subdural hemorrhage

Appendix table 8 Modified Arterial Occlusive Lesion Classification

Grade	Description
0	primary occlusive lesions remains same
1	debulking of thrombus without recanalization
2	partial or complete recanalization of the primary lesion with thrombus/occlusion in the distal vascular tree
3	complete recanalization of the primary occlusion with no thrombus in the vascular tree or beyond the primary occlusive lesions

Appendix table 9 Collateral Score

Category	Score	Description
None	0	Absent collaterals
Poor	1	Collaterals filling ≤50% of the occluded territory
Intermediate	2	Collaterals filing >50%, but <100% of the occluded territory
Good	3	Collaterals filling 100% of the occluded territory

Appendix table 10 Description of Subgroup Types and Definitions

	Subgroups	**Number of levels**	**Levels**
1	Age (Years)	3	18-60; 60-80; ≥80
2	Baseline NIHSS	3	2-15; 16-19; ≥20
3	Quartiles of time from onset of symptoms to randomization	4	Min-Quartile 25%; >Quartile 25%-Quartile 50%; >Quartile 50%-Quartile 75%; > Quartile 75% (if applicable)
4	Quartiles of time from onset of symptoms to groin puncture	4	Min-Quartile 25%; >Quartile 25%-Quartile 50%; >Quartile 50%-Quartile 75%; > Quartile 75% (if applicable)
5	Quartiles of time from randomization to groin puncture	4	Min-Quartile 25%; >Quartile 25%-Quartile 50%; >Quartile 50%-Quartile 75%; > Quartile 75% (if applicable)
6	Quartiles of time from onset of symptoms to revascularization	4	Min-Quartile 25%; >Quartile 25%-Quartile 50%; >Quartile 50%-Quartile 75%; > Quartile 75% (if applicable)
7	Quartiles of time from randomization to revascularization	4	Min-Quartile 25%; >Quartile 25%-Quartile 50%; >Quartile 50%-Quartile 75%; > Quartile 75% (if applicable)
8	Ipsilateral extracranial carotid tandem lesion	2	Yes; No
9	Occlusion location	3	ICA; M1; M2
10	Collaterals	2	Grade 0-1; Grade 2-3
11	Large vessel occlusion due to different etiologies	3	Intracranial atherosclerosis; Cardioembolism; Others