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STATISTICAL AND EPIDEMIOLOGICAL ANALYSIS PLAN (SEAP) FOR NON-INTERVENTIONAL STUDIES (NIS)

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BI Study Number:	0135-0349
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Title:	Effectiveness and safety of IV rt-PA treatment in Chinese AIS patients aged above 80 years: a real-world study
Brief lay title:	Alteplase treatment in elderly AIS patients
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NIS Statistician [SEAP author]	[redacted]
NIS [redacted] [SEAP reviewer]	[redacted]
NIS Data [redacted] [SEAP reviewer]	[redacted]

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2. LIST OF ABBREVIATIONS

AIS	Acute Ischaemic Stroke
ASD	Absolute Standardised Difference
BI	Boehringer Ingelheim
CDE	Centre for Drug Evaluation
CSCA	Chinese Stroke Centre Alliance
DMRP	Data Management and Review Plan
GPP	Good Pharmacoepidemiology Practice
ICH	Intracranial Haemorrhage
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
IVT	Intravenous Thrombolysis
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NIS	Non-Interventional Study(ies)
PS	Propensity Score
PSM	Propensity Score Matching
RCT	Randomised Controlled Trials
RR	Relative Risk
rt-PA	Recombinant Tissue Plasminogen Activator
RWE	Real-World Evidence
SOP	Standard Operation Procedure
ZSQCC	Zhejiang Stroke Quality Control Centre

3. RESPONSIBLE PARTIES

NIS Statistician [SEAP author]

[redacted]

SEAP reviewers are:

- BI NIS [redacted] [SEAP reviewer] (in all cases)
- NIS Data [redacted] [SEAP reviewer] (in all cases)
- RWE CoE [SEAP reviewer] (for all globally initiated studies and for local studies) involving BI products and Global NIS not involving BI products,
- TSTAT (for NISnd only)
- TM Epi [SEAP reviewer] (When BI NIS [redacted] is not TM Epi; in all cases)

4. PURPOSE AND SCOPE

This is a complete statistical and epidemiological analysis plan for the research about whether Chinese AIS patients older than 80 years can benefit from IV rt-PA treatment within 4.5 hours of symptom onset in a real-world clinical setting, including the effectiveness and safety. More detailed and explicit statistical analysis methods and procedures are presented here, especially the Propensity Score Matching method.

5. AMENDMENTS AND UPDATES

None

6. RESEARCH QUESTION AND OBJECTIVE

Research question: Can Chinese AIS patients older than 80 years benefit from IV rt-PA treatment within 4.5 hours of symptom onset in a real-world clinical setting?

Primary objective:

- To compare the 1-year neurological functional outcome (as measured by modified Rankin Scale [mRS] score) of Chinese AIS patients aged > 80 years who received IV rt-PA treatment within 4.5 hours of symptom onset versus those who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive reperfusion therapy.

Secondary objectives:

- To compare in-hospital and other 1-year clinical outcomes (including any intracranial haemorrhage (ICH), all-cause mortality during hospitalisation, independence (mRS 0-2) at 1 year, distribution of mRS score at 1 year, and all-cause mortality at 1 year. Detailed description of these outcomes are provided in the section “secondary outcomes”) of elderly AIS patients who received IV rt-PA treatment within 4.5 hours of symptom onset versus those who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive any reperfusion therapy.
- To compare the baseline characteristics of AIS patients aged > 80 years treated with IV rt-PA within 4.5 hours of symptom onset versus AIS patients aged > 80 years who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive reperfusion treatment in the ZSQCC platform to evaluate potential channelling.

7. RESEARCH METHODS

7.1 STUDY DESIGN

This is a NIS based on existing data. We will analyse data of AIS patients aged > 80 years in China collected from the ZSQCC platform.[P2104780],[P2104783],[P2104784],[P2104779],[P2104782]

At least 1301 or 1146 AIS patients in total are planned to be enrolled to this study, calculated by 2:1 or 1:1 treatment ratio, respectively.

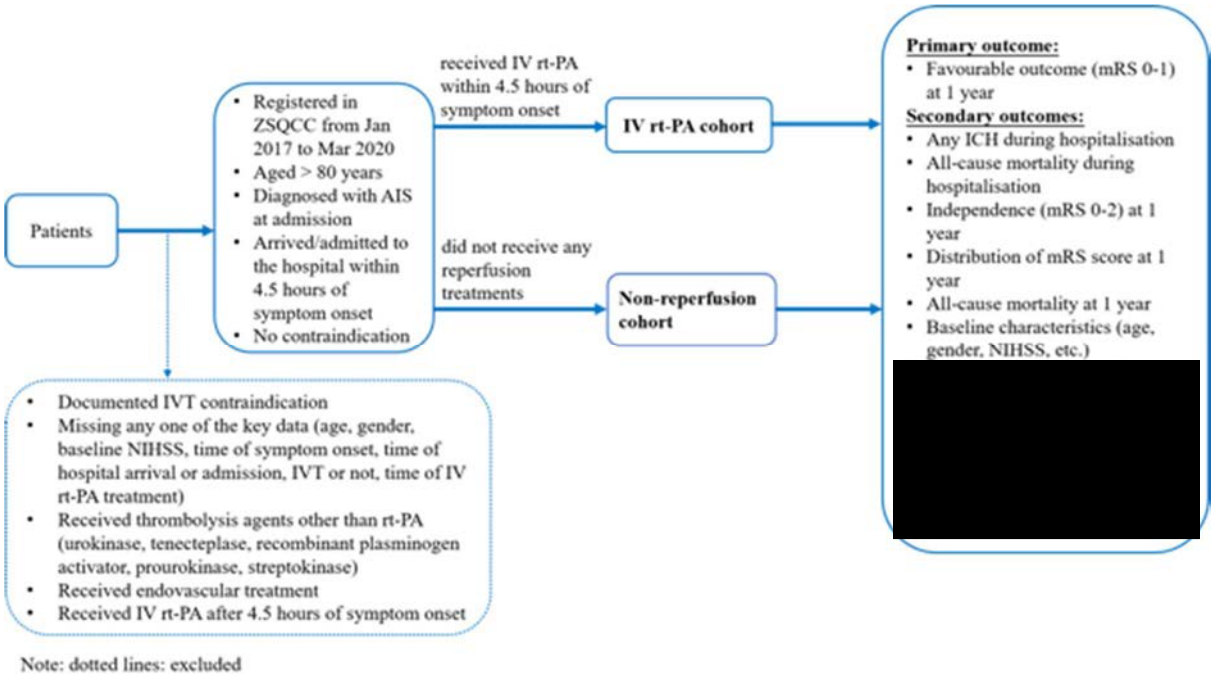
Patients meeting the inclusion/exclusion criteria will be divided into 2 cohorts:

- IV rt-PA cohort: AIS patients aged > 80 years who received IV rt-PA within 4.5 hours of symptom onset
- Non-reperfusion cohort: AIS patients aged > 80 years who arrived or admitted to the hospital within 4.5 hours of symptom onset and did not receive any reperfusion treatments

Propensity score matching (PSM) will be used to match the baseline characteristics between the above 2 cohorts. Clinical outcomes and baseline characteristics will be compared between the matched cohorts.

The flow of data selection for each of the 2 reporting patient cohorts is depicted in Figure 1 below.

Figure 1 Patient cohorts selected for the non-interventional study



7.2 SETTING

In this study, AIS patient data from 80 stroke centres in the ZSQCC platform from January 2017 to March 2020 will be used.

7.3 STUDY POPULATION

No sampling will be undertaken and all patients who meet all the inclusion criteria and none of the patients presenting with at least one exclusion criterion will be included.

The inclusion and exclusion criteria are listed below:

Inclusion criteria:
- Patients registered in the ZSQCC platform from Jan 2017 to Mar 2020
- > 80 years of age
- Diagnosed with AIS at admission
- Arrived or admitted to the hospital within 4.5 hours of symptom onset
- If treated with IV rt-PA: received IV rt-PA within 4.5 hours of symptom onset

Exclusion criteria:
- Documented IVT contraindication except age to IV rt-PA treatment according to the SmPC.
- Missing any one of the key data (age, gender, baseline National Institutes of Health Stroke Scale [NIHSS], time of symptom onset, time of hospital arrival or admission, IVT or not, time of IV rt-PA treatment)
- Received thrombolysis agents other than rt-PA (urokinase, tenecteplase, recombinant plasminogen activator, prourokinase, streptokinase)
- Received endovascular treatment
- Received IV rt-PA after 4.5 hours of symptom onset

7.4 STUDY VISITS

Not applicable.

8. VARIABLES

8.1 EXPOSURES

The exposure of this study is IV rt-PA treatment within 4.5 hours of symptom onset.

8.2 OUTCOMES

8.2.1 Primary outcomes

- Favourable outcome (mRS 0-1) at 1 year

8.2.2 Secondary outcomes

- Any intracranial haemorrhage (ICH) during hospitalisation
- All-cause mortality during hospitalisation
- Independence (mRS 0-2) at 1 year
- Distribution of mRS score at 1 year
- All-cause mortality at 1 year
- Baseline characteristics (age, gender, NIHSS, etc.)

8.3 COVARIATES

The covariates to be collected at baseline as follows:

- Demographic and sociological characteristics
  - Age
  - Gender (male, female)
  - Body weight
  - Medical insurance status (urban employee basic medical insurance, urban resident basic medical insurance, new rural cooperative medical insurance, other insurance, no insurance)
- Lifestyle related characteristics
  - Smoking status (current smoker, former smoker, never smoker)
- Stroke severity (baseline NIHSS)
- Time from symptom onset to hospital admission
- For patients in the IV rt-PA cohort:
  - Time from symptom onset to treatment
  - Time from hospital admission to treatment
  - rt-PA dosage (dichotomised as standard dosage and low dosage)
- Comorbidities at baseline
  - Diabetes
  - Coronary artery disease
  - Atrial fibrillation

- Prior stroke/transient ischaemic attack
- Hypertension

- Co-medication at baseline
  - Anti-platelet
  - Oral anticoagulation
  - Lipid lowering
- Hospital level
  - Grade 2
  - Grade 3

Other covariates including:

- Duration of hospitalization
- Reasons for not being treated with rt-PA for rt-PA non treatment group

9. DATA SOURCES

9.1 ZSQCC PLATFORM

The current study will be conducted based on data from the ZSQCC platform, which is a continuous comprehensive reporting system that collects 100000 patient-level data from 80 stroke centres from January 2017 to March 2020.

All printed medical documents for consecutive AIS patients admitted in the stroke centre will be provided and scanned by investigators from ZSQCC. Only the de-identified scanned documents will be preserved as images in a safe information database. The local infrastructure and characteristics of each recruited centre will also be recorded.

The database includes patient demographic information, baseline clinical characteristics, indicators related to diagnosis and treatment during hospitalisation and follow-up after discharge. The platform staffs tried to follow up all discharged patients by a phone call at 1-year discharge. In addition, patients who received rt-PA treatments were followed up by a phone call at 3-month after discharge. Telephone follow-up of the platform was conducted by platform staffs. The follow-up standards were unified, and telephone recordings were all kept. Neurologists conducted trainings at regular intervals for platform staffs and randomly checked the telephone recordings. Several studies based on this dataset were approved by the Second Affiliated Hospital of Zhejiang University Institutional Review Board (IRB) and were published in peer-reviewed journals.[P2104780],[P2104783],[P2104784],[P2104779],[P2104782]

9.2 CSCA PLATFORM

The CSCA is a national, hospital-based, multicentre, voluntary, multifaceted intervention and continuous quality improvement initiative, launched by Chinese Stroke Association in 2015. This programme is made available to all Chinese grade 2 and 3 hospitals. Hospitals continued to join the programme in a staggered manner. By Jul 2019, 1476 hospitals (720 grade 2 hospitals, 756 grade 3 hospitals) had participated into this programme. Hospital characteristics, including geographic region, teaching status, hospital volume (grade 2 and 3) and annual stroke volume, are surveyed. Data were collected via the web-based patient data collection and management tool ([redacted]), abstracted via chart review, coded, de-identified and transmitted in a secure manner to maintain patient confidentiality compliant with national privacy standards. The following data were collected for each hospitalization: patient demographics, history of disease and medication, hospital presentation, initial neurological status, medications and interventions, reperfusion strategy and in-hospital outcomes and complications.

10. DATA MANAGEMENT AND SOFTWARE/TOOLS

10.1 SOFTWARE/TOOLS

Propensity score matching (PSM) will be performed using R 4.0.5 (package: MatchIt) and other analyses will be conducted with SAS 9.4.

10.2 HANDLING OF MISSING VALUES

For comorbidities at baseline (including diabetes, coronary artery disease, atrial fibrillation, prior stroke/transient ischaemic attack, and hypertension) and co-medication at baseline (including anti-platelet, oral anticoagulation, and lipid lowering), missing values will be regarded as absence of those comorbidity and co-medication. For medical insurance status, smoking status, and hospital level, missing values will be assigned to a separate group.

10.3 HANDLING OF INCONSISTENCIES IN DATA AND OUTLIERS

Inconsistencies in Data and Outliers will be re-checked. If they are still abnormal (for example: age > 120; gender is neither male nor female), they will be removed from the analysis.

11. DATA ANALYSIS

11.1 MAIN ANALYSIS

Descriptive data regarding patient demographic, lifestyle-related, and clinical characteristics will be summarized. For categorical measures, data will include the frequency (number of patients with specific cases [n]) and percentage (%) of total study patients observed in each category (N). All variables will be summarized descriptively by tabular displays of mean, standard deviations, median, inter-quartile ranges, and ranges of continuous variables, and frequency distributions of categorical variables. When necessary, continuous variables also will be categorized into intervals, with the distribution of patients (n, N, %) for each interval provided. We will compare the baseline characteristics of the 2 treatment cohorts (patients who received IV rt-PA and patients who did not receive reperfusion treatment) through the absolute standardized difference (ASD) method, where at least 0.1 ASD will be considered a significant difference.

To account for potential confounding, the 2 cohorts will be 1:1 or 2:1 matched by baseline characteristics using the Propensity Score Matching method. The feasibility of PSM will be evaluated based on available sample size and descriptive results. If patient characteristic between the 2 cohorts are significantly different, i.e., less than 50% of patients in the IV rt-PA cohort can be matched to the non reperfusion cohort based on PSM, the study design will be re-evaluated before proceeding to analysis.The PSM aims to balance the 2 cohorts on baseline covariates. The propensity score model will include age, gender, baseline NIHSS/ NIHSS categories (0-4, 5-10, 11-15, 16-21, and $\geqslant$ 22), medical insurance status, smoking status, hospital level, diabetes, coronary artery disease, atrial fibrillation, prior stroke/transient ischaemic attack, hypertension, anti-platelet, lipid lowering, oral anticoagulation, and time from symptom onset to hospital admission. The method of Nearest Neighbour matching will be used (a maximum caliper width equal to 0.2 of the standard deviation of the logit of the propensity score) to select the matched samples. Then we will compare the baseline characteristics of the 2 propensity-score-matched cohorts. The absolute standardized difference (ASD) between the 2 PS-matched cohorts will be calculated, where at least 0.1 ASD will be considered a significant difference. For baseline covariates that are not sufficiently balanced after PSM, they will be included in an appropriate multivariate model to adjust for those differences.

For the primary outcome, a comparison of the percentage of 1-year* mRS score (0-1) between the 2 PS-matched cohorts will be conducted using a Chi-square test. A conditional logistic regression model will be used to estimate odds ratios (95% confidence interval) between the 2 matched cohorts.

For the secondary outcomes, descriptive summaries will be conducted in the PS-matched cohorts separately. For the categorical variables including any intracranial haemorrhage (ICH) during hospitalisation, all-cause mortality during hospitalisation and independence (mRS 0-2) at 1 year, the Chi-square test and conditional logistic regression model will be conducted. For the distribution of mRS score at 1 year, the Wilcoxon rank sum test and ordinal logistic regression model will be performed. For the all-cause mortality at 1 year, in addition to a Chi-square test, a Kaplan-Meier curve with log-rank test will be used to analyse the data. Cox regression models will be used to estimate hazard ratios (95% confidence interval) between the 2 matched cohorts.

*Note: 1 year in this analysis is defined as 12±1 months.

11.3 SAFETY ANALYSIS

This is a NIS based on existing data. From safety information collecting and reporting perspective, this study will not involve individual medical record review, thus no adverse event/adverse drug reaction information is required to collect. The analysis refers to Section 10.1.

12. QUALITY CONTROL

The statistical analytic approach and programming code will be reviewed/repeated by a second analyst.

13. REFERENCES

13.1 PUBLISHED REFERENCES

P21-04780 Zhang CC, Lou M, Chen ZC, Chen HF, Xu DJ, Wang ZM, Hu HF, Wu CL, Zhang XL, Ma XD, Wang YX, Hu HT. Analysis of intravenous thrombolysis time and prognosis in patients with in-hospital stroke. J Zhejiang Univ (Med Sci). 2019; 48(3):260-266.

P21-04783 Chen HF, Gong XX, Xu DJ, Wang ZM, Hu HF, Wu CL, Zhang XL, Ma XD, Wang YX, Hu HT, Lou M, Chen ZC. Advanced treatment time improves outcomes of patients with ischemic stroke undergoing reperfusion therapy. J Zhejiang Univ (Med Sci). 2019; 48(3):247-253.

P21-04784 Zhong WS, Chen ZC, Chen HF, Xu DJ, Wang ZM, Hu HF, Wu CL, Zhang XL, Ma XD, Wang YX, Hu HT, Lou M. Effects of emergency medical service on prognosis of ischemic stroke patients treated with intravenous thrombolysis. J Zhejiang Univ (Med Sci). 2019; 48(3):241-246.

P21-04779 Pan FH, Lou M, Chen ZC, Chen HF, Xu DJ, Wang ZM, Hu HF, Wu CL, Zhang XL, Ma XD, Wang YX, Hu HT. Effect of different working time on the prognosis of ischemic stroke patients undergoing intravenous thrombolysis. J Zhejiang Univ (Med Sci). 2019; 48(3):267-274.

P21-04782 Tao AY, Wang ZM, Chen HF, Xu DJ, Hu HF, Wu CL, Zhang XL, Ma XD, Wang YX, Hu HT, Lou M. Association of atrial fibrillation with hemorrhagic transformation after intravenous thrombolysis in patients with ischemic stroke. J Zhejiang Univ (Med Sci). 2019; 48(3):254-259.

13.2 UNPUBLISHED REFERENCES

None.

ANNEX 1. ADDITIONAL INFORMATION

None.

ANNEX 2. REVIEWERS AND APPROVAL SIGNATURES

The NIS SEAP must be sent for review to the following individuals **prior to approval**.

Reviewer	**NIS involving BI product(s)**	**NIS not involving BI product(s)**	
		Global NIS	**Local NIS**
NIS[redacted]	X	X	X
Global TM Epi*	X	X	X
NIS Data[redacted]	X	X	X
TSTAT (for NISnd only)	X	X	X
RWE CoE	X	X	

** When BI NIS lead is not TM Epi*

Study Title: Effectiveness and safety of IV rt-PA treatment in Chinese AIS patients aged above 80 years: a real-world study

Study Number: 0135-0349

Protocol Version: 1.0

I herewith certify that I agree to the content of the study SEAP and to all documents referenced in the study SEAP.

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____