Boehringer Ingelheim

Statistical and Epidemiological Analysis Plan (SEAP) for Non-Interventional Studies (NIS)

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Title:	Temporal trends of thrombolysis treatment in Chinese acute ischemic stroke (AIS) patients from 2007-2017: analysis of China National Stroke Registry (CNSR) I, II, and III
Brief lay title:	Trends of thrombolysis treatment in China from 2007 to 2017
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NIS Statistician [SEAP author]	[redacted]
NIS [redacted] [SEAP reviewer]	[redacted]
NIS Data [redacted] [SEAP reviewer]	[redacted]

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

AF	Atrial fibrillation
AIS	Acute ischemic stroke
BI	Boehringer Ingelheim
CI	Confidence interval
CNSR	China National Stroke Registry
CRC	Clinical research coordinator
CRF	Case report form
CRO	Contract research organization
DM	Diabetes mellitus
DMRP	Data management and review plan
DTN	Door-to-needle time
EDC	Electronic data collection
[redacted]	[redacted]
ICH	Intracranial hemorrhage
IQR	Interquartile range
IS	Ischemic stroke
IV-rtPA	Intravenous recombinant plasminogen activator
IVT	Intravenous thrombolytics
MI	Myocardial infarction
MOH	Ministry of Health
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NCRCND	National Clinical Research Center for Neurological Diseases
NIHSS	National Institutes of Health Stroke Scale
NIS	Non-interventional study
OTT	Onset-to-treatment time
PRF	Paper-based registry form
SAH	Subarachnoid hemorrhage
SEAP	Statistical and epidemiological analysis plan
SD	Standard deviation
TIA	Transient ischemic attack

3. RESPONSIBLE PARTIES

NIS Statistician [SEAP author]

[redacted]

SEAP reviewers are:

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

4. PURPOSE AND SCOPE

The purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the data.

This SEAP assumes familiarity with the protocol, including protocol amendments (if presents) and its supplementary materials. In particular, the SEAP is based on the planned analysis specification as written in the protocol Section 9 "Research Methods". Therefore, SEAP reviewers may consult the protocol for more background information on the study, e.g., on study rational and background, study objectives, study design and population, inclusion and exclusion criteria, definition of measurements, covariates and expected outcomes.

5. AMENDMENTS AND UPDATES

NA

6. RESEARCH QUESTION AND OBJECTIVE

Research Question:
Whether the quality of IV-rtPA treatment thrombolysis treatment has been improved with the continuous development of stroke centers and stroke care quality control networks supported by academic society and MOH during the last decade in China?

Primary Objectives:

- To investigate the temporal changes in the proportion of IV-rtPA treatment from 2007 to 2017 among intravenous thrombolytics (IVT) eligible patients and overall AIS patients in China;
- To investigate the temporal changes in IV-rtPA treatment time intervals from 2007 to 2017 among IV-rtPA treated patients in China.

Secondary Objectives:

- To describe the demographic and clinical characteristics of the IV-rtPA treated patients, IVT eligible patients and the overall AIS patients from the CNSR I to III.

7. RESEARCH METHODS

7.1 STUDY DESIGN

The Chinese treatment guideline for AIS was updated in 2010 where the recommended time window for intravenous recombinant plasminogen activator (IV-rtPA) treatment was extended from 3h since symptoms onset to 4.5h. Along with the development of stroke centers and stroke care quality control system, in order to understand the impact of these efforts on the clinical practices for AIS treatment in China, this study is designed to evaluate the temporal changes from 2007 to 2017, in the IV-rtPA treatment proportion and treatment time intervals of AIS patients.
This study is designed to be non-interventional and exploratory, while the 10-year time window was made possible by combining existing data from three cross-sectional surveys of AIS patients in China: CNSR I (2007-2008), II (2012-2013), and III (2015-2017).

Patients in each of the CNSR waves will be divided into 3 major groups respectively: (1) all AIS patients, (2) IVT-eligible patients (arrival within2h & 3.5h since symptom onset and without documented absolute contraindication), and (3) IV-rtPA-treated patients (treatment within 3h & 4.5h since symptom onset). This stratification allows calculation and description of IV-rtPA treatment proportion and treatment time intervals across the 10-year window. Taken together the demographic and clinical characteristics data embedded in the CNSR studies, the analysis will help to answer the research question, and hope to provide understanding of the gap between clinical practice and guideline recommendation for acute phase stroke care, and to provide evidence linking minimized in-hospital delays for IV thrombolysis with improved AIS outcomes.

7.2 SETTING

This study will use AIS patient data from CNSR I to III, stretching across a 10-year time frame from 2007 to 2017. CNSR is a nationwide, prospective stroke registry where patients with acute cerebrovascular diseases were continuously enrolled for 8-12 month every 5-year since 2007. [redacted]

CNSR I (2007-2008) was conducted in 131 sites across China, including 113 tertiary and 18 urban hospitals, all the included ischemic stroke (IS) patients were older than 18 and within 14 days of onset. CNSR II (2012-2013) was conducted in 219 hospitals nationwide, and all the included IS patients were older than 18 and within 7 days of onset. CNSR III (2015-2017) was conducted in 201 hospitals, AIS or TIA patients aged 18 years and older within 7 days of symptom onset were included.

STUDY POPULATION

All eligible patients from the CNSR I to III will be included. It was estimated that in CNSR I, II, and III, the number of total AIS patient is 12415, 19604, and 15204, respectively.

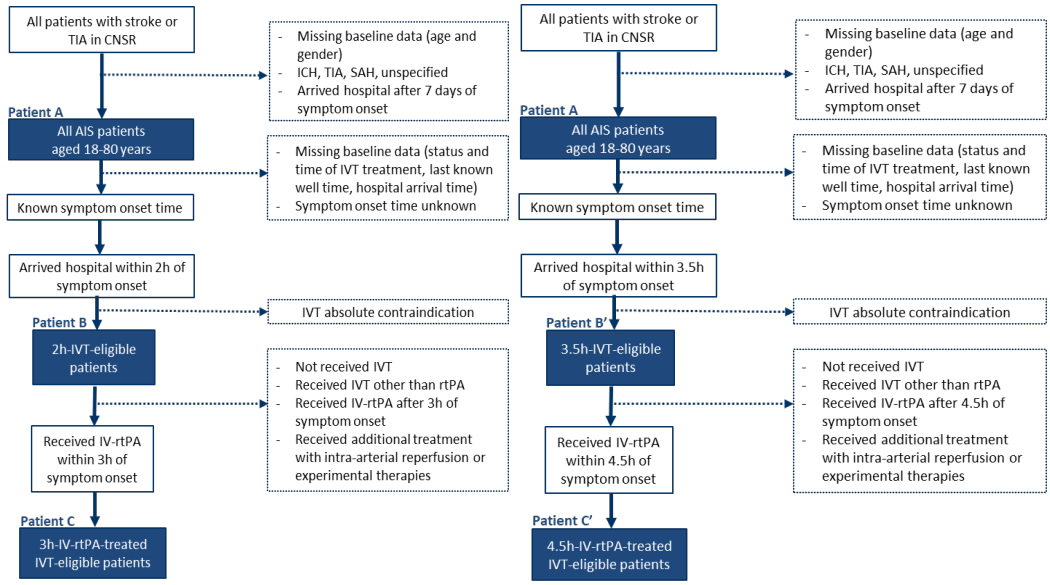
The study will analyze data for the following patient groups:

(1) <u>All AIS patients (patient group A):</u> the overall AIS patients aged 18-80 years who arrived at hospital within 7 days of symptom onset;

(2) <u>IVT-eligible patients (patient groups B and B')</u>:
Patient group B and B' are subsets of patient group A: AIS patients who arrived at hospital within 2h (patient group B) and 3.5h (patient group B') of symptom onset and with no documented absolute contraindications to IVT treatment;

(3) <u>IV-rtPA-treated patients (patient groups C and C'):</u>
Patient group C is a subgroup of patient group B, while patient group C' is a subset of patient group B': IVT-eligible patients who arrived at hospital within 2h of symptom onset and received IV-rtPA within 3h of symptom onset (patient group C) and those who arrived at hospital within 3.5h of symptom onset and received IV-rtPA within 4.5h of symptom onset (patient group C').

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



(a) Patient groups A, B, and C (b) Patient groups A, B', and C'

Figure 1.Patient groups selected for the time-trend study

The in- and exclusion criteria for each of the reporting groups are listed below:

All AIS patients (patient group A)

<u>Inclusion criteria:</u>

1. Aged 18-80 years
2. Diagnosed with AIS on admission

Exclusion criteria:

1. Missing baseline data including age and gender
2. Diagnosed with intracranial hemorrhage (ICH), Transient Ischemic Attack (TIA), subarachnoid hemorrhage (SAH), or unspecific stroke
3. Arrived at hospital after 7 days of symptom onset

IVT-eligible patients (patient groups B and B')

Inclusion criteria:

1. Met the in- and exclusion criteria of "all AIS patients" (Group A)
2. Arrived at hospital within 2h (patient group B) or 3.5h (patient group B') of symptom onset

Exclusion criteria:

1. Missing key data including
   I. symptom onset time (or last known well time);
   II. hospital arrival time;
   III. whether received IVT treatment or not;
   IV. the time of IVT treatment
2. Documented IVT absolute contraindications, according to the case report form (CRF) for each of CNSR

IVT Absolute Contraindications according to CRFs for each of CNSR:

For CNSR I:

- Aged above 80 years;
- CT evidence of intracranial haemorrhage;
- CT evidence of early signs of large cerebral infarction;
- Concurrence of epileptic seizures during ischemic stroke;
- Have suffered a stroke or severe head injury in the past 3 months;
- Uncontrolled hypertension despite active treatment. Uncontrolled hypertension refers to systolic blood pressure > 185 mmHg or diastolic blood pressure > 110 mmHg, measured at least 10 minutes apart and repeated 3 times;
- Known haemorrhagic condition with significant bleeding disorder at onset or within the past 6 months;
- Acute pancreatitis or proven ulcerative gastrointestinal disease within 3 months;
- Recent invasive cardiopulmonary resuscitation or childbirth within 10 days. Non stress vascular puncture (such as subclavian vein or femoral vein puncture);
- Blood glucose < 50 mg/dl (2.7 mmol/l) or > 400 mg/dl (22.2 mmol/l);
- Platelet count < 105/mm3;
- Prothrombin time (PT) (international normalized ratio [INR]) > 1.5 or PT > 15 or activated partial thromboplastin time (APTT) > 40 sec.

For CNSR II and III:

- Uncontrolled hypertension despite active treatment. Uncontrolled hypertension refers to systolic blood pressure > 185 mmHg or diastolic blood pressure > 110 mmHg;
- Concurrence of epileptic seizures during ischemic stroke;
- Recent surgery or trauma within 15 days;

- Recent intracranial or spinal surgery, head trauma, or stroke within 3 months;
- Previous history of intracranial haemorrhage, aneurysm, vascular malformation, or brain tumour;
- Active visceral bleeding within 22 days;
- Platelet count <105/mm3, APTT (after heparin treatment) > 40 sec, PT > 15 or PT (INR) > 1.7, or known haemorrhagic condition/suspected subarachnoid haemorrhage;
- CT evidence of ICH, SAH, or signs of large infarction.

IV-rtPA-treated patients (patient groups C and C')

Inclusion criteria:

1. Met the in- and exclusion criteria of "IVT-eligible patients"
2. Treated with IV-rtPA within 3h (patient group C) or 4.5h (patient group C') of symptom onset

Exclusion criteria:

1. Not received IVT
2. Received IVT other than rtPA
3. Treated with IV-rtPA after 3h (group C) or 4.5h (group C') of symptom onset
4. Received additional treatments with intra-arterial reperfusion or experimental therapies

7.3 STUDY VISITS

This study examines the time window from symptom onset to hospital arrival and IV-rtPAtreatment time (i.e. whether and when IV-rtPA treatment is issued to IVT-eligible patients). This is a non-interventional study based on existing data from CNSR registry, and no new data are collected nor are new study visits.

8. VARIABLES

8.1 EXPOSURES

The study is descriptive in nature. It will not assess the association between any exposure and outcomes.

8.2 OUTCOMES

8.2.1 Primary outcomes

For all the three waves of CNSR, the following primary outcomes will be assessed:

- Proportion of patients who received IV-rtPA treatment within 3h of symptom onset (patient group C) among 2h IVT-eligible patients (patient group B);
- Proportion of patients who received IV-rtPA treatment within 4.5h of symptom onset (patient group C') among 3.5h IVT-eligible patients (patient group B').

8.2.2 Secondary outcomes

Among all AIS patients (patient group A) for all three waves of CNSR:

- Proportion of patients who arrived at hospital within 2h of symptom onset and who received IV-rtPA treatment within 3h of symptom onset (patient group C);
- Proportion of patients who arrived at hospital within 3.5h of symptom onset and who received IV-rtPA treatment within 4.5h of symptom onset (patient group C');

Among 3h IV-rtPA patients (patient group C) for all three waves of CNSR:

- The door-to-needle (DTN) time (time between arrival at hospital and the administration of IV-rtPA treatment);
- Proportion of patients DTN time ≤ 60 minutes (min);
- Time between symptom onset and arrival at hospital;
- Time between symptom onset and the administration of IV-rtPA treatment.

Among 4.5h IV-rtPA patients (patient group C') for all three waves of CNSR:

- The DTN time;

- Proportion of patients DTN time ≤ 60 min;
- Time between symptom onset and arrival at hospital;
- Time between symptom onset and the administration of IV-rtPA treatment.

9. DATA SOURCES

The current study will be conducted based on data collected from the three waves of CNSR, where patients with acute cerebrovascular diseases were enrolled every 5 year from 2007 till 2017.

CNSR I (2007-2008) used data from 131 sites across China, including 113 tertiary and 18 urban hospitals, all the included ischemic stroke (IS) patients were older than 18 and within 14 days of onset. Paper based registry forms (PRF) were used for data collection. Patient information including demographics (age, gender, etc.), NIHSS, medical history (diabetes mellitus, hypertension, coronary heart disease/previous myocardial infarction, atrial fibrillation, previous stroke, TIA, dyslipidemia), symptom onset to door time, health insurance schemes (urban basic medical insurance schemes for urban and governmental employees and urban residents, new rural cooperative medical schemes for rural residents, commercial insurance, and self-payment), vascular risk factors, imaging (mainly magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA)), blood sampling, time related variables (symptom onset time, hospital arrival time, CT time, IV rtPA treatment time, etc.), implementation of performance measures for acute stroke care, final diagnosis, length of stay, in hospital death, and follow up information for 3 month, 6 month, and 12 month was collected. Hospital level information including geographic region (e.g., east, central, or west, according to the annual report on health statistics of China)), teaching status, hospital bed size, and annual stoke volume was collected.

CNSR II (2012-2013) used data from 219 hospitals in China, and all the included IS patients were older than 18 and within 7 days of onset. Web based case report forms (CRF) were used for data collection. Patient information including demographics, NIHSS, medical history, symptom onset to door time, health insurance schemes, vascular risk factors, imaging, blood sampling, time related variables, implementation of performance measures for acute stroke care, final diagnosis, length of stay, modified Rankin scale at discharge, and in hospital death was collected. Follow-up information for 3 month, 6 month, and 12-month was collected by phone interview. Hospital level information including geographic region, teaching status, hospital bed size, and annual stoke volume was collected.

CNSR III (2015-2017) used data from 201 hospitals in China, where AIS or TIA patients aged 18 years and older within 7 days of symptom onset were included for the study. An electronic data collection (EDC) system was used to collect data. Patient information including demographics, NIHSS, medical history, symptom onset to door time, health insurance schemes, vascular risk factors, imaging, blood sampling, time related variables, implementation of performance measures for acute stroke care, final diagnosis, length of stay, modified Rankin scale at discharge, and in hospital death was collected. Follow-up information for 3 month, 6 month, and 12 month was collected by phone interview. Hospital level information including geographic region, teaching status, hospital bed size, and annual stoke volume was collected.

10. DATA MANAGEMENT AND SOFTWARE/TOOLS

For this study, the data will be managed by the Data Management Group of NCRCND. Source code of data management and data analyses will be kept for inspection for at least five years after publication of the results.

10.1 SOFTWARE/TOOLS

Data management, tabulations, and graphics will be carried out with SAS version 9.4 software (SAS institute).

10.2 HANDLING OF MISSING VALUES

Every reasonable attempt have been undertaken to ensure completeness of data collection. In general, missing data will be treated as missing. No data imputation will be performed for the missing data. The amount of missing data will be reported and its effect on potentially bias conclusions will be assessed. Due to the nature of existing data, the interpretation is based on non-missing data.

10.3 HANDLING OF INCONSISTENCIES IN DATA AND QUTLIERS

Missing and erroneous values in patient cases can significantly impact the ability to perform research for identifying risk factors and disease distribution, treatment progression. This study is mainly based on review of data collected from CNSR I, II, III and aims at evaluating differences in clinical practice of IV-rtPA treatment among AIS patients from 2007 to 2017. Data follow-up period has already been finished. Thus, data cannot meet the criteria of this study will be excluded.

Exclusion criteria:

1. Missing key data including
   - symptom onset time (or last known well time);
   - hospital arrival time;
   - whether received IVT treatment or not;
   - the time of IVT treatment
   - age and gender
2. Contradiction of time period:
   - IVT treatment time earlier than symptom onset time (or last known well time);
   - treatment time earlier than hospital arrival time;
   - hospital arrival time earlier than symptom onset time
3. Diagnosed with intracranial hemorrhage (ICH), Transient Ischemic Attack (TIA), subarachnoid hemorrhage (SAH), or unspecific stroke
4. Arrived at hospital after 7 days of symptom onset

11. DATA ANALYSIS

The study is descriptive in nature. The calculation will be based on the available data.

[redacted]

For continuous data, descriptive statistics (number of patients, mean, standard deviation [SD], minimum, median, interquartile range, and maximum) will be presented. Categorical data will be presented as frequency and proportion with 95% CI as appropriate.

11.1 MAIN ANALYSIS

Patient group A includes patients aged 18-80 years and diagnosed with AIS on admission. Patients with missing baseline data including age and gender and diagnosed with intracranial hemorrhage (ICH), Transient Ischemic Attack (TIA), subarachnoid hemorrhage (SAH), or unspecific stroke and arrived at hospital after 7 days of symptom onset will be excluded.

Patient group B and patient group B' are both based on patient group A. And patients with missing key data will be excluded from patient group B and patient group B', including symptom onset time or last known well time, hospital arrival time, whether received IVT treatment or not and the time of IVT treatment.
Patients documented with IVT absolute contraindications, according to the case report form (CRF) for each of CNSR will be also excluded from patient group B and patient group B'.
Patients group B included patients who arrived at hospital within 2h of symptom onset.
Patients group B' included patients who arrived at hospital within 3.5h of symptom onset.

Patient group C is based on patients group B and patient group C' is based patient group B'. And both patient group C and patients group C' are to meet the inclusion criteria of "IVT-eligible patients". Patients not received IVT or received IVT other than rtPA or received additional treatments with intra-arterial reperfusion or experimental therapies will be excluded. Patients group C included patients who were treated with IV-rtPA within 3h.
Patients group C' included patients who were treated with IV-rtPA within 4.5h.

11.1.1 Primary outcomes

For all the three waves of CNSR, the following primary outcomes will be assessed:(Table 1
Proportion of 3 h IV-rtPA treatment among 2h IVT eligible patients & 4.5h IV-rtPA treatment among 3.5h IVT eligible patients)

- Proportion of patients who received IV-rtPA treatment within 3h of symptom onset (patient group C) among 2h IVT-eligible patients (patient group B);
- Proportion of patients who received IV-rtPA treatment within 4.5h of symptom onset (patient group C') among 3.5h IVT-eligible patients (patient group B').

[redacted]

11.1.2 Secondary outcomes

Among all AIS patients (patient group A) for all three waves of CNSR: (Table 3.1 Proportion of 3h IV-rtPA treatment within 2h of symptom onset arrival and Proportion of 4.5 h IV-rtPA treatment within 3.5h of symptom onset arrival among Among all AIS patients)

- Proportion of patients who arrived at hospital within 2h of symptom onset and who received IV-rtPA treatment within 3h of symptom onset (patient group C);
- Proportion of patients who arrived at hospital within 3.5h of symptom onset and who received IV-rtPA treatment within 4.5h of symptom onset (patient group C');

Among 3h &4.5h IV-rtPA patients (patient group C) for all three waves of CNSR:(Table 3.2 DTN time, onset-to-door, onset-to-needle time and Proportion of DTN time less than 60 minutes among 3h & 4.5h IV-rtPA patients)

- The door-to-needle (DTN) time (time between arrival at hospital and the administration of IV-rtPA treatment);
- Proportion of patients DTN time ≤ 60 minutes (min);
- Time between symptom onset and arrival at hospital;
- Time between symptom onset and the administration of IV-rtPA treatment.

[redacted]

[redacted]

11.3 SAFETY ANALYSIS

Not applicable.

12. QUALITY CONTROL

For the CNSR, safety and risk control were assessed by the Data Safety and Monitoring Board (DSMB) before the study. All hospitals participating in the CNSR were selected by a Steering Committee using a convenient sampling method from the China National Network of Stroke Research developed by the National Center of Quality Management in Stroke Care. Clinical research associates conducted data verification on site during the study. Data management team of NCRCND performed remote real time data supervision for all the data cleaning, integration, analysis, and other processing.

The internal data validity of CNSR I, II, and III were ensured by employing trained clinical research coordinators (CRCs) to guarantee the quality of data entry. Independent contract research organizations (CROs) were invited to monitor the study procedures and to ensure the quality of data entry. All data elements collected by PRF, web-based CRF, or EDC system were manually or mechanically checked for completeness, coding correctness, and appropriateness of the diagnostic algorithm. A professional data processing company was responsible for the computer or PAD data entry.
For this study, the standard operation procedures (SOPs) of Boehringer Ingelheim (BI), such as NIS SOP, will be strictly followed. In addition, key elements of the International Society for Pharmacoepidemiology Good Pharmacoepidemiology Practices (GPP) will be followed. The statistical analysis method will be reviewed and repeated by a second analyst. All the data cleaning, integration, analysis, and other processing will be conducted under the guidance and supervision of data management team of NCRCND. The study report will be reviewed, approved, and archived per SOPs of BI.

13. REFERENCES

13.1 PUBLISHED REFERENCES

Not applicable.

13.2 UNPUBLISHED REFERENCES

Not applicable.

ANNEX 1. ADDITIONAL INFORMATION

1、DEFINITION OF VARIABLES

2、DICTIONARY OF VARIABLES

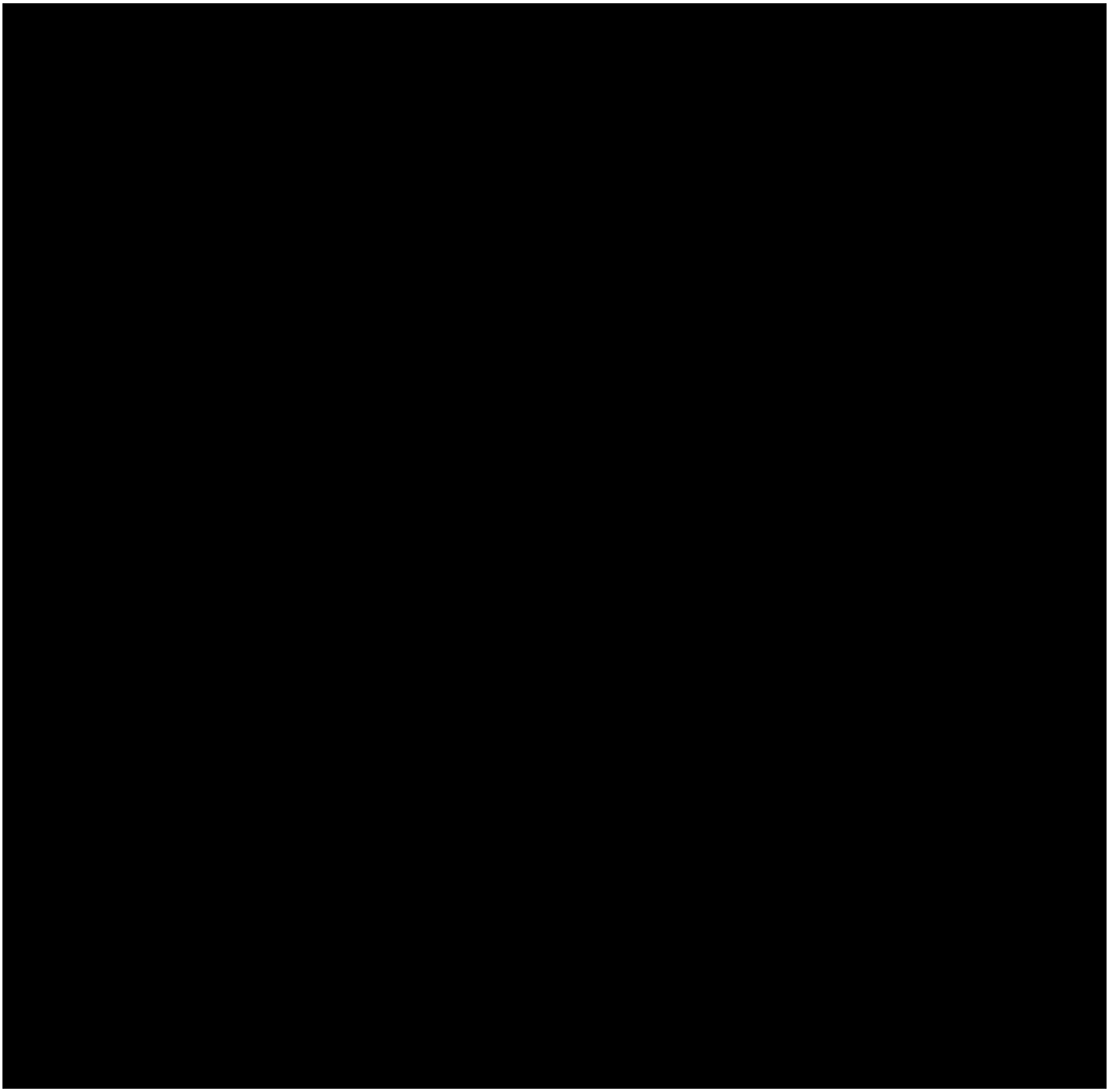
	Variable Name	Type	Label & Value
1	Wave	character	Study wave of CNSR 1 2 3
[redacted]			
3	hosp_id	character	Hospital ID
[redacted]			
5	hosp_name	character	Hospital Name
[redacted]			
19	onset_arriv_hour	numerical	Hours From Onset To Hospital Arrival
20	arriv_tpa_hour	numerical	Hours From Hospital Arrival To Tpa Treatment
21	ONSET_TPA_hour	numerical	Hours From Onset To Tpa Treatment
22	TPA_AC	numerical	Absolute Contraindications For Tpa: 0=No;1=Yes

3、MOCK TABLE&FIGURE

Primary outcomes:

Table 1 Proportion of 3 h IV-rtPA treatment among 2h IVT eligible patients & 4.5h IV-rtPA treatment among 3.5h IVT eligible patients

Patients	ALL	CNSR1	CNSR2	CNSR3
3h IV-rtPA / 2h IVT eligible	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)
4.5h IV-rtPA / 3.5h IVT eligible	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)



Secondary outcomes:

Table 3.1 Proportion of 3h IV-rtPA and Proportion of 4.5 h IV-rtPA treatment among all AIS patients

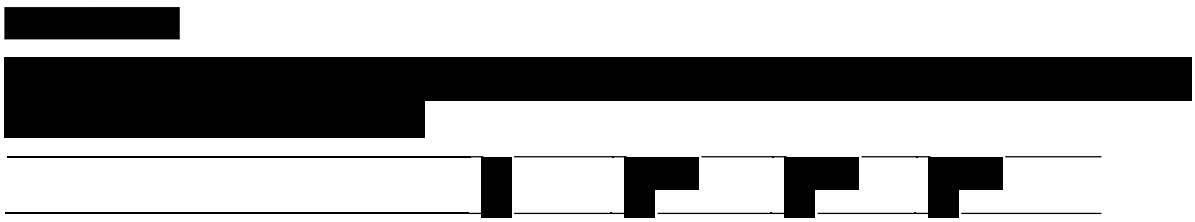
Proportion	ALL	CNSR1	CNSR2	CNSR3
3h IV-rtPA /all AIS patients	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)
4.5h IV-rtPA /all AIS patients	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)

Table 3.2.1 DTN time, onset-to-door, onset-to-needle time and Proportion of DTN time less than 60 minutes among 3h IV-rtPA patients

	All N=	CNSR1 N=	CNSR2 N=	CNSR3 N=
DTN time (minutes)				
	Median(IQR) (MIN,MAX) Mean(SD))	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)
DTN ≤ 60 minutes % Onset-to-door (minutes)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)
	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)
Onset-to-needle time(minutes)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)

Table 3.2.2 DTN time, onset-to-door, onset-to-needle time and Proportion of DTN time less than 60 minutes among 4.5h IV-rtPA patients

	All N=	CNSR1 N=	CNSR2 N=	CNSR3 N=
DTN time (minutes)				
	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)
DTN ≤ 60 minutes % Onset-to-door (minutes)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)
	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)
Onset-to-needle time(minutes)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)	Median(IQR) (MIN,MAX) Mean(SD)



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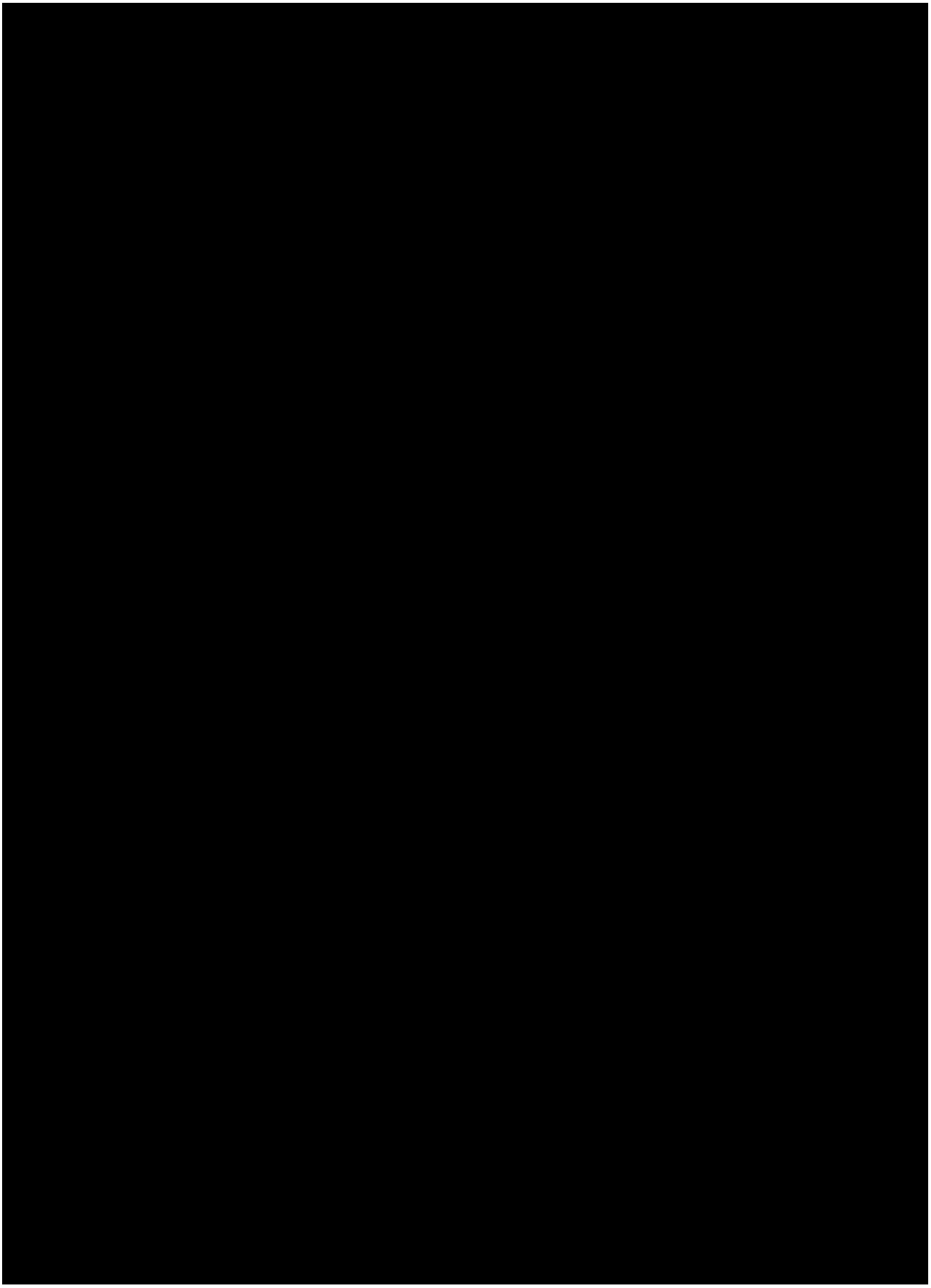

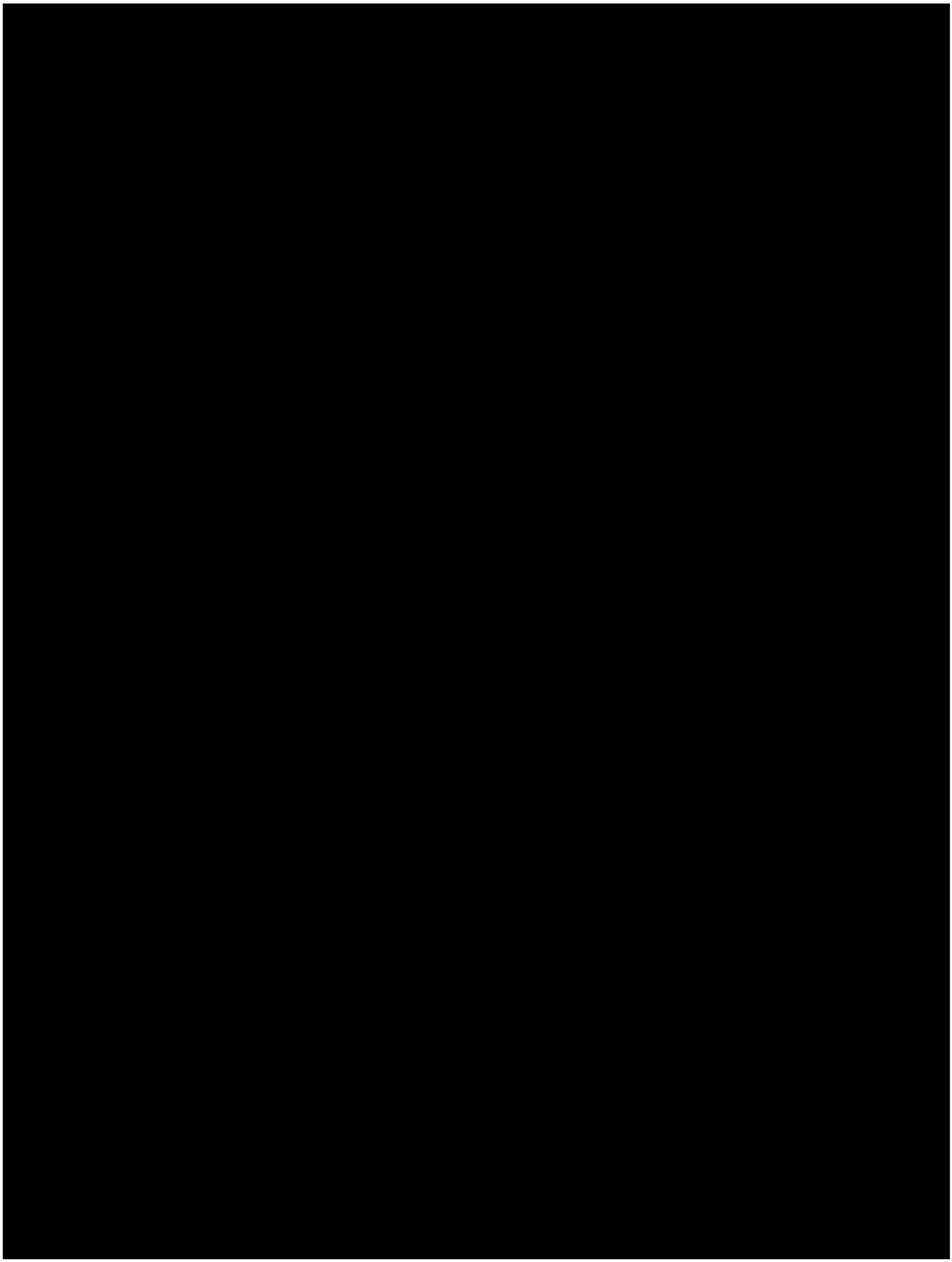

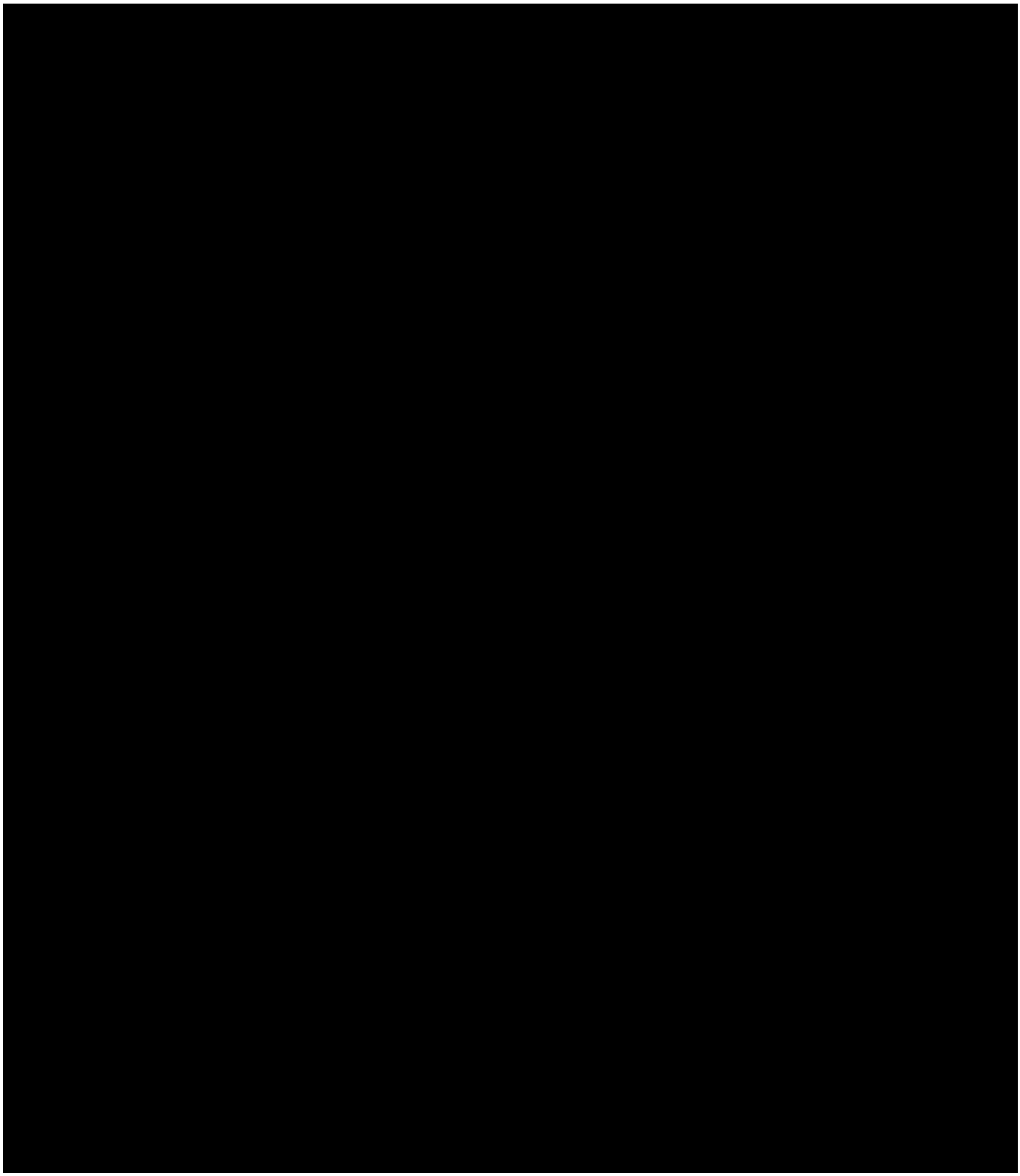

ANNEX 2. REVIEWERS AND APPROVAL SIGNATURES

Study Title: Temporal trends of thrombolysis treatment in Chinese acute ischemic stroke (AIS) patients from 2007-2017: analysis of China National Stroke Registry (CNSR) I, II, and III

Study Number: 0135-0343

Protocol Version: V1.1

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**:** _____

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

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