Statistical Analysis Plan:

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Postsurgical Initiation of Thromboprophylaxis in patients with Cushing's Disease (PIT-CD): A randomized controlled trial

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Sponsor:

Huashan Hospital Affiliated to Fudan University.

Signature Page

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of terms
AE	Adverse Event
BMI	Body Mass Index
CI	Confidence Interval
CTA	Computed Tomography Angiography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Magnetic Resonance Angiography
NCI	National Cancer Institute
PE	Pulmonary Embolism
pH	Potential of Hydrogen
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TRAE	Treatment-Related Adverse Event
TRSAE	Treatment-Related Serious Adverse Event
UFC	Urine Free Cortisol
ULN	Upper Limit of Normal
VTE	Venous ThromboEmbolism

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is developed based on the most recent study protocol (version 5.0, 01-Jul-2021) and electronic Case Report Form (eCRF, version 2.0, 01-Jul-2021), and details the statistical analysis strategies and methods for the study.

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

1.1 Study Design

This is a multi-center, prospective, randomized parallel-controlled study.
This is an open-label study, but the primary efficacy outcomes will be assessed by an independent evaluation committee (Core-lab), who will remain blinded to the group assignments.
Study design is presented as below (Figure 1):

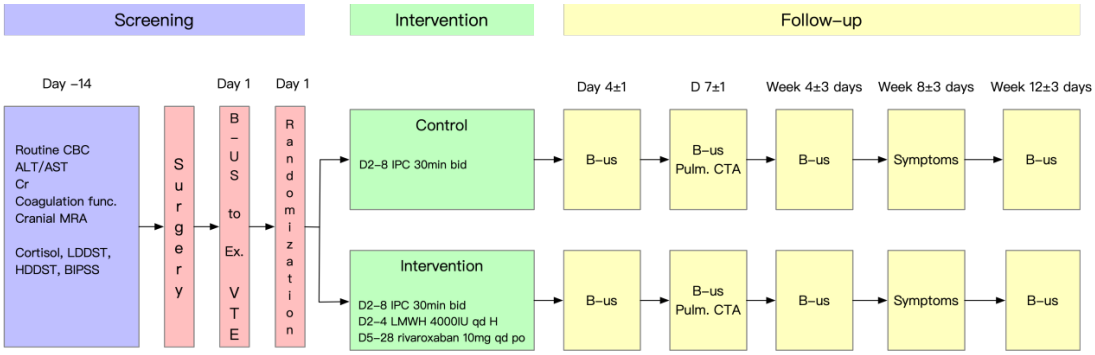

Figure 1. Study schema

1.2 Study Objectives

Primary objective:

- To assess whether the combined prophylaxis group is superior to the mechanical prophylaxis group in reducing the incidence of VTE within 12 weeks after surgery in patients with Cushing's disease.

Secondary objective:

- To compare the incidence of deep vein thrombosis (DVT) within 12 weeks post-surgery between the combined prophylaxis group and the mechanical prophylaxis group in patients with Cushing's disease;
- To compare the incidence of pulmonary embolism (PE) within 12 weeks post-surgery between the combined prophylaxis group and the mechanical prophylaxis group in patients with Cushing's disease;
- To compare the incidence of symptomatic VTE within 12 weeks post-surgery between the combined prophylaxis group and the mechanical prophylaxis group in patients with Cushing's disease;

- To compare the incidence of embolism-related mortality within 12 weeks post-surgery between the combined prophylaxis group and the mechanical prophylaxis group in patients with Cushing's disease;
- To compare the incidence of all-cause mortality within 12 weeks post-surgery between the combined prophylaxis group and the mechanical prophylaxis group in patients with Cushing's disease;
- To assess the safety of combined prophylaxis, including major bleeding, minor bleeding, coagulation abnormalities, and thrombocytopenia.

1.3 Study endpoints

Primary efficacy outcome:

- Incidence of venous thromboembolism (VTE) within 12 weeks after surgery.

Secondary efficacy outcomes:

- Incidence of DVT within 12 weeks after surgery;
- Incidence of PE within 12 weeks after surgery;
- Incidence of symptomatic DVT, symptomatic PE, or symptomatic VTE within 12 weeks after surgery;
- Incidence of VTE-associated mortality within 12 weeks after surgery;
- All-cause mortality within 12 weeks after surgery.

Safety outcomes:

- Major bleeding;
- Minor bleeding;
- Hemorrhage-associated surgery;
- Hemorrhage-associated readmission;
- Coagulation disorders;
- Thrombocytopenia;
- Increase in liver function.

1.4 Estimation of Sample Size

Our estimates are based on a retrospective study examining the effects of preventive anticoagulation during the perioperative period in Cushing syndrome. This study reported that the incidence of postoperative VTE was lower in patients receiving preventive anticoagulants (6%) compared to those who did not (20%). Therefore, we assume that the incidence of the primary outcome in the control group is 20%, while in the intervention group it is 5% within 12 weeks. Based on these assumptions, the required sample size for each group is 93, with an alpha level of 0.05 and a power of 0.9. Accounting for an estimated 10% dropout rate, the total number of patients needed is 206.

1.5 Randomization

The study utilizes the central randomization system to dynamically randomize patients into groups. The main stratification factors during the randomization process include: center, disease duration, age, and gender. Subjects will be randomly assigned in a 1:1 ratio, with the intervention group receiving mechanical prophylaxis combined with low-molecular-weight heparin/rivaroxaban, and the control group receiving mechanical prophylaxis only.

1.6 Study Procedure

The study consists of 3 stages: screening period, intervention period, and follow-up period. See study protocol for details.

2 STATISTICAL ANALYSIS METHODOLOGY

2.1 Statistical Analysis Variables

This SAP will include variables to be analyzed as follows: demographics and baseline characteristics, drug exposure, concomitant medications, treatment efficacy and safety data.

2.1.1 Demographics and baseline characteristics

The demographic and baseline information will at least include age (years), gender, ethnicity, medical history, concomitant medication, height (cm), weight (kg), body mass index (kg/m^2), cranial magnetic resonance angiography (MRA) or computed tomography angiography (CTA), ECG test, chest X-ray or pulmonary CT, lower limb venous ultrasound, peripheral oxygen saturation, 8 AM serum cortisol, 24-hour urine cortisol, blood gas analysis and CTA (if peripheral oxygen saturation below 95%) at baseline.

The medical history includes prior pituitary adenoma surgery, prior radiation therapy history, allergy history and other medical history.

2.1.2 Extent of exposure and compliance

2.1.2.1 Study treatment

In the intervention group, the pharmacological agents used include enoxaparin and rivaroxaban.

- Enoxaparin Sodium Injection: The dosage is 4000 IU once daily (subcutaneous injection), administered for 3 days (starting on postoperative day 2 and continuing until postoperative day 4).
- Rivaroxaban Tablets: The dosage is 10 mg once daily (oral administration) for 24 days (from postoperative day 5 until day 28).

2.1.2.2 Concomitant medication

Concomitant therapy is defined as all medication other than the study treatment administered to a patient coinciding with the study treatment period, which include medications (other than study drugs) starting on or after the start date of study surgery or medications starting prior to the start date of study surgery and continuing after the start date of study surgery.

2.1.3 Efficacy outcomes

2.1.3.1 Primary efficacy outcome

- Incidence of venous thromboembolism (VTE) within 12 weeks after surgery.

VTE is defined as either deep vein thrombosis (DVT) or pulmonary embolism (PE), regardless of whether the cases are symptomatic or asymptomatic.

2.1.3.2 Secondary efficacy outcomes

- Incidence of DVT within 12 weeks after surgery;

- Incidence of PE within 12 weeks after surgery;
- Incidence of symptomatic DVT, symptomatic PE, or symptomatic VTE within 12 weeks after surgery;
- Incidence of VTE-associated mortality within 12 weeks after surgery;
- All-cause mortality within 12 weeks after surgery.

"Symptomatic" is defined as the presence of one or more of the following symptoms attributed to VTE: pain or swelling in the affected leg; chest pain, dyspnea, or decreased oxygen saturation.

2.1.4 Safety

2.1.4.1 Safety outcomes

- Major bleeding;
- Minor bleeding;
- Hemorrhage-associated surgery;
- Hemorrhage-associated readmission;
- Coagulation disorders;
- Thrombocytopenia;
- Elevated transaminase levels.

Major bleeding is defined according to the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis [1]. This includes: fatal bleeding; bleeding that is symptomatic and occurs in a critical area or organ; extrasurgical site bleeding causing a fall in hemoglobin level of 20g/L or more, or leading to transfusion of two or more units of whole blood or red cells; surgical site bleeding that requires a second intervention.

2.1.4.2 Adverse events (AEs)

This study focuses on the treatment emergent adverse events (TEAEs), which were defined as any AEs occurring at or after the study surgery.

The adverse events in this study primarily include bleeding (such as non-injection site bruising, nosebleeds, hematuria, gastrointestinal bleeding, hematoma, intracranial hemorrhage, and retroperitoneal bleeding). Adverse reactions related to rivaroxaban include neutropenia, thrombocytopenia, hepatocellular injury, jaundice, cholestasis, allergic reactions, and Stevens-Johnson syndrome. Adverse reactions associated with enoxaparin include thrombocytopenia and thrombocytosis, cutaneous vasculitis, and skin necrosis.

All AEs terms will be coded using MedDRA 27.0 or higher version before study database lock. MedDRA SOC and PT will be presented in the summary tables.

Severity of AEs

The severity of AE will be classified by the categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.

Causal relationship between AE and study treatment

Relationship between AEs and study treatment, the investigator will evaluate the

possible association between adverse events and study treatment according to the time relationship and its clinical judgment in terms of "definitely related", "possibly related", "possibly unrelated", "definitely unrelated" and "unable to determine". Among which, events whose causal relationship is judged as "definitely related", "possibly related" or "unable to determine" will be considered as related to the study treatment. If a relationship to the study treatment was missing, the analysis was considered to be related to the study treatment when appropriate.

Definition of serious adverse events

A serious adverse event (SAE) refers to an untoward medical occurrence that at any dose meets any of the following criteria: 1) results in death; 2) is life-threatening; 3) requires inpatient hospitalization or prolongation of existing hospitalization; 4) results in persistent or significant disability/incapacity; 5) is a congenital anomaly/birth defect; 6) is an important medical event.

2.1.4.3 Vital signs

The following vital signs measurement will be collected and recorded in the eCRF: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beat/min), breathing rate (beat/min), axillary temperature (℃) and oxygen saturation (%).

They will be performed at screening, 24 hours after surgery, day 4 ± 1d, week 4 ± 3d post-surgery, and week 12 ± 3d post-surgery.

2.1.4.4 Laboratory test

The following laboratory tests items will be collected and recorded in the eCRF:

Hematology: hemoglobin, platelet counts, and white blood cell counts;

Blood chemistry: alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin, creatinine, urea nitrogen, potassium, sodium, calcium;

Urinalysis: urine leukocyte, and urine erythrocyte;

Fecal occult blood: red blood cells, and occult blood;

Coagulation: prothrombin time, activated partial thromboplastin time, thrombin time, D-dimer, fibrinogen quantification and international normalized ratio;

Blood gas analysis: pH, oxygen saturation, oxygen partial pressure and carbon dioxide partial pressure.

The hematology, blood chemistry, urinalysis, fecal occult blood and coagulation assessment will be performed at screening, 24 hours after surgery, day 4 ± 1d, week 4 ± 3d post-surgery, and week 12 ± 3d post-surgery.

The blood gas analysis assessment will be performed at day 7 ± 1d. If peripheral oxygen saturation is below 95%, blood gas analysis assessment will be added at screening, 24 hours after surgery, week 4 ± 3d post-surgery and week 12 ± 3d post-surgery.

2.1.4.5 Endocrine test

The following endocrine test items will be collected and recorded in the eCRF:

8 AM serum cortisol, 24-hour urine free cortisol (UFC), prolactin, growth hormone, insulin-like growth factor-1, follicle-stimulating hormone, luteinizing hormone, estradiol, testosterone, free triiodothyronine, free thyroxine, triiodothyronine, thyroxine and thyroid stimulating hormone.

The endocrine test will be performed at screening, 24 hours after surgery, week 4 ± 3d post-surgery, and week 12 ± 3d post-surgery.

2.1.4.6 Lower limb venous ultrasound

The lower limb venous ultrasound test will be performed at screening, 24 hours after surgery, day 4 ± 1d post-surgery, day 7 ± 1d post-surgery, week 4 ± 3d post-surgery, and week 12 ± 3d post-surgery.

2.1.4.7 Pulmonary CTA

The pulmonary CTA test will be performed at day 7 ± 1d. If peripheral oxygen saturation is below 95%, blood gas analysis assessment will be added at screening, 24 hours after surgery, week 4 ± 3d post-surgery and week 12 ± 3d post-surgery.

2.2 Statistical Analysis Sets

The analysis sets will be based on Full analysis Set (FAS), per protocol set (PPS) and safety set (SS).

2.2.1 Full analysis set

FAS include all enrolled subjects who have used the study treatment and completed at least one efficacy evaluation.

2.2.2 Per protocol set

A subset of FAS, consisting of subjects who strictly followed the trial protocol, completed the entire clinical observation, and filled out the eCRF as required.

2.2.3 Safety set

SS includes all subjects who have received the study treatment and have undergone at least one safety evaluation.

2.3 Statistical Methods

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

For summary statistics, mean, median and quartiles will be reported to one more decimal place than the original data, while the standard deviation and the confidence interval (CI) will be reported to two more decimal places. 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 generally keep one decimal. Percent of zero counts will not be shown and only the integer 100 will be displayed when the percentage is 100%. The p values will keep 4 decimal or will be displayed as "<0.0001" or ">0.9999" for extreme values.

2.3.1 Subject disposition

The total number of screened subjects and the number and proportion of subjects by treatment groups who were randomized, received study surgery, received study treatment, completed the study treatment and discontinued the study early will be provided. The reasons for screening failures will be listed descriptively.

When appropriate, the number and proportion of subjects of overall dropout rates and dropout rates due to adverse events will be provided, and the comparison between groups will be conducted with the use of Chi-squared test or Fisher's exact test.

2.3.2 Demography and baseline characteristics

Based on FAS, demographic data will be summarized by treatment groups as follows:

- Age (years);
- Gender (female vs. male);
- Ethnicity (the Han nationality, and other);
- Weight (kg);
- Height (cm);
- Body mass index (BMI, kg/m^2) = weight (kg)/height^2 (m).

In addition, prolactin, free thyroxine, thyroid stimulating hormone, 8 AM serum cortisol, 24-hour urine free cortisol and disease duration will also be summarized by treatment groups.

2.3.3 Medical history

Based on FAS, the number and percentage of subjects with prior pituitary adenoma surgery, prior radiation therapy history, allergy history and other medical history will be summarized by treatment groups descriptively.

2.3.4 Concomitant medication

Concomitant medications will be listed based on SS.

2.3.5 Extent of exposure and compliance

Based on SS, actual cumulative dose and compliance were summarized by study treatment.

Actual cumulative dose and compliance

The actual cumulative dose of a study treatment is defined as the total tablets given during the study treatment exposure minus remaining tablets and will be summarized for each of the study treatment group.

Compliance will be calculated as follows:

Compliance (%) = actual number of tablets / planned number of tablets * 100.

The planned number of tablets is defined as the total number of tablets dispensed to the subjects during the study treatment exposure period.

2.3.6 Efficacy analysis

All efficacy data analyses will be conducted based on FAS; for primary and secondary outcome analysis, PPS will also be used as a supportive role.

2.3.6.1 Primary outcome

For the incidence of VTE within 12 weeks after surgery, the number and percentage of subjects will be summarized by treatment group, and both unstratified and stratified analyses will be performed. The primary analysis will be conducted by using the Cochran-Mantel-Haenszel test, stratified by stratification factors including gender (male vs. female), age (≤35 vs. >35) and disease duration (≤2 years vs. >2 years). A supportive unstratified analysis will be conducted using Pearson's Chi-squared test (or Fisher's exact test where appropriate). The common risk difference along with 95% CI will be estimated using the Mantel-Haenszel method for the stratified analysis, while the unstratified risk difference will be calculated using standard method. Final interpretation of treatment effects will be based on stratified results.

Additional sensitivity analyses will be conducted for the primary outcome. We will count all time from randomization until the VTE event, death, end of trial, drop out, or withdrawal of consent, whichever comes first for each study subject. First, Kaplan-Meier cumulative event curves will be constructed to estimate the probability of the primary endpoint by time after randomization within treatment groups. Second, if there is no violation of the proportional hazards assumption, we will also use the Cox proportional hazard model to estimate relative treatment effects after controlling for baseline factors that might influence the rate of the primary endpoint, e.g. stratified by the following stratification variables: gender (male vs. female), age (≤35 vs. >35) and disease duration (≤2 years vs. >2 years) for a more efficient estimate of relative treatment effects. The hazard ratio of the intervention group versus the control group with CIs will be provided.

2.3.6.2 Secondary outcomes

For the incidence of DVT within 12 weeks after surgery, incidence of PE within 12 weeks after surgery, incidence of symptomatic DVT, symptomatic PE, or symptomatic VTE within 12 weeks after surgery, incidence of VTE-associated mortality within 12 weeks after surgery and all-cause mortality within 12 weeks after surgery, they will be analyzed with the same method as that used for the primary outcome.

2.3.6.3 Subgroup analyses

Subgroup analyses will be conducted for the primary outcome using the primary analysis method based on prespecified baseline factors as follows but not limited to:

- Center (pooled centers if necessary);
- Gender (male vs. female);
- Age (≤35 vs. >35);
- Disease duration (≤2 years vs. >2 years);
- 24h UFC (<5 x ULN vs. ⩾5 x ULN);
- BMI (≤30 vs. >30)

The output results will be displayed on a forest plot, including the p-values for heterogeneity corresponding to the interaction term between intervention and each subgroup variable.

2.3.7 Safety analysis

In this study, the safety analysis will be mainly based on statistical description unless otherwise specified. All of the safety data analyses will be performed in SS.

2.3.7.1 Analysis of safety outcomes

For the incidence of major bleeding, incidence of minor bleeding, incidence of hemorrhage-associated surgery, incidence of hemorrhage-associated readmission, incidence of coagulation disorders, incidence of thrombocytopenia, incidence of increase in liver function, the number and percentage of subjects will be summarized by treatment group, and in order to signal potential safety problems, the Chi-squared test or Fisher's exact test will be used to compare the incidence difference between groups. Additionally, the rate with 95% Clopper-Pearson CIs and rate difference with 95% exact CIs will be calculated as appropriate.

2.3.7.2 Analysis of AEs

The number and percentage of subjects with any TEAEs, treatment-related adverse events (TRAEs), treatment emergent serious adverse events (TESAEs), treatment-related serious adverse events (TRSAEs), TEAEs leading to withdrawal from the trial will be summarized and analyzed as classified by SOC and PT by treatment groups. Descriptive analysis for adverse events will include but not limited to:

- Any TEAEs summarized by SOC and PT;
- Severity of TEAEs summarized by SOC and PT;
- Grade 3 or higher TEAEs summarized by SOC and PT;
- Any TRAEs summarized by SOC and PT;
- Severity of TRAEs summarized by SOC and PT;
- Grade 3 or higher TRAEs summarized by SOC and PT;
- Any TESAEs and TRSAEs summarized by SOC and PT;
- Severity of TESAEs and TRSAEs summarized by SOC and PT;
- All TEAEs and TRAEs leading to withdrawn summarized by Severity by SOC and PT;

A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple severity grades for the same preferred

term will be summarized under the maximum severity grade recorded for the event. AE with missing severity grade will be included in the 'grade 3 or higher' column of the summary tables.

The data listings will be provided for all AEs and SAEs.

The Chi-squared test or Fisher's exact test will be used to compare the difference between groups when appropriate.

2.3.7.3 Analysis of vital signs

Vital signs data will be summarized by presenting summary statistics of the observed value and change from baseline by treatment group and visit.

2.4 Data Processing Conventions

2.4.1 Baseline definition

In this study, baseline values are defined as those data collected before intervention (within 24 hours after surgery 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

Missing data will not be imputed unless stated otherwise.

For primary endpoint, in case of non-negligible amounts of missing data (≥5%) noted, we will use the Monte Carlo Markov Chain method based on the missing at random assumption to impute missing data. Separate imputations will be performed by randomized treatment arm. The regression model will include gender, age, disease duration, baseline BMI and 24h UFC. If percentage of missing primary endpoint is less than 5%, multiple imputation will not be performed on missing data and they will be regarded as no event occurrence.

When start date of an AE was partially or completely missing, it is considered to be a TEAE unless there was clear evidence that the AE occurred before the first dosing.

When end date of concomitant medications was partially or completely missing, it is considered to be concomitant medications.

2.4.3 Time window

For the incidence of VTE at week 12 ± 3d post-surgery, observed measurements for out-of-window visits will be analyzed as if a VTE occurred within week 12. For all other outcomes, no visit window adjustments will be applied and data recorded at the nominal visit will be presented.

2.4.4 Unscheduled visits

Except for shift tables and the summary of worst post-baseline result, unscheduled visits will not be included in summary, unless otherwise specified.

3 CHANGES TO PLANNED ANALYSES FROM THE PROTOCOL

No changes of planned analyses in the protocol are made in this statistical analysis plan.

4 INTERIM ANALYSIS

The Data Safety Monitoring Board (DSMB) plans to conduct the interim analysis meeting after randomization and 12-week follow-up are completed for 103 subjects. The significance level for interim analysis is set at 0.001 according to the Haybittle-Peto boundary principle.

Based on these analyses, the DSMB will advise the steering committee on whether the randomized comparisons in this study have demonstrated clearly beneficial of the intervention. If the p-values from the interim analysis for both groups are less than 0.001, recruitment will be halted, and the study will meet the criteria for early termination. If the p-values are greater than or equal to 0.001, recruitment will continue to achieve the planned sample size, with the final analysis significance level set at 0.049.

5 STATISTICAL ANALYSIS SOFTWARE

All statistical analyses and data summary will be carried out by using SAS® 9.4 and R 4.4.1 in this study.

6 REFERENCES

[1] Schulman, S., et al., *Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients.* J Thromb Haemost, 2010. **8**(1): p. 202-4.

7 APPENDIX

None.