Statistical Analysis Plan

Protocol Title:

Varian ProBeam Proton Therapy System China Clinical Trial (Hefei)

SAP Version & Date: V1.0，2022-11-11

Sponsor:	Varian Medical System Trading (Beijing) Co., Ltd
Clinical trial Leading site:	Anhui Provincial Hospital

Directory

Abbreviations

Abbreviations	Full spelling in English	Chinese translation
ADL	Activities of Daily Living	Activities of daily living
AE	Adverse Event	Adverse events
ATC	Anatomical Therapeutic Chemical	Anatomy, Therapy, Chemistry
CI	Confidence Interval	confidence interval
CR	Complete Response	Complete remission
CT	Computed Tomography	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate	Tumor disease control rate
DOR	Duration of Response	Sustained time to remission
ECOG	Eastern Cooperative Oncology Group	Eastern Oncology Collaborative Group
FAS	Full Analysis Set	Full analysis set
ICH	The International Council for Harmonisation of Technical Requirement for Pharmaceuticals for Human Use	International Harmonization Council for Technical Requirements for Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Activities	Medical Dictionary of Regulatory Activities
NYHA	New York Heart Association	New York Heart Society
OIS	Oncology Information System	Oncology Information System
ORR	Objective Response Rate	Objective response rate
PD	Progressive Disease	Disease progression
PET	Positron Emission Tomography	Positron emission tomography
PN	Preferred Name	Preferred name
PPS	Per-Protocol Set	Conforms to the scenario set
PR	Partial Response	Partial relief
PSA	Prostate Specific Antigen	Prostate-specific antigens
PT	Preferred Terms	Preferred term
SAE	Serious Adverse Events	Serious adverse events
SAP	Statistical Analysis Plan	Statistical analysis plan
SAS	Statistical Analysis System	Statistical analysis system
SD	Stable Disease	Stable disease
SLD	Sum of Longest Diameter	Sum of longest diameters of tumors
SOC	System Organ Class	Systematic organ classification
SS	Safety Set	Security datasets
TEAE	Treatment Emergent Adverse Event	Adverse events during the treatment period
TNM	Tumor, Node, Metastasis	Tumors, lymph nodes, metastases
WHODD	World Health Organization Drug Dictionary	World Health Organization Dictionary of Medicines

WOCF	Worst Observation Carried Forward	Worst observed data carryover

This statistical analysis plan (SAP) refers to the E9 guiding principles of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance for Industry: Statistical Principles for Clinical Trials ICH E3 Guidance for Industry: Structure and Content of Clinical Study Reports Relevant national regulations and guidelines, according to the clinical study protocol titled "Varian ProBeam Proton Therapy System China Clinical Trial (Hefei)" (version number: V1.4, Version Date:2022-06-10) developed.

This SAP describes the rules for the presentation and analysis of short-term follow-up efficacy data and safety evaluation data specified in the protocol, and describes in detail the data, variables and statistical methods that need to be summarized and analyzed. Unless otherwise specified, the final analysis of short-term follow-up will be performed in accordance with this plan, and the presentation of statistical analysis results may be fine-tuned to some extent during the statistical analysis phase.

This SAP was established and finalized prior to the locking of this clinical trial database.

1 Overview of the trial

1.1 Objective

1.1.1 Primary purpose

To evaluate whether the main efficacy evaluation index of Probeam in radiation therapy for cancer patients reached the target value of the disease control rate (DCR) 3 months after the end of the last treatment. Whether the proportion of CTCAE grade 3 toxicity was lower than the acceptable value, and whether CTCAE grade 4 and 5 toxicity occurred.

1.1.2 Secondary purpose

To evaluate the secondary efficacy of Probeam in radiation therapy for cancer patients, objective response rate (ORR), duration of response (DOR), DCR at 1 month after the end of last treatment, tumor markers (if required), tumor-specific symptoms, The reality of the product usability assessment.

To evaluate the proportion of CTCAE grade 1 and 2 toxicity, laboratory tests, ECOG physical condition classification, tumor recurrence rate, adverse event rate, serious adverse event rate, and device defect incidence of Probeam in radiation therapy for cancer patients.

1.2 Trial design

This trial is a prospective, two-center, single-group target-value experimental design.

Prospective: Adopt a research approach that starts now and tracks the future. Prospective studies can clarify the causal relationship, and there are unified standards for diagnosis, detection, and evaluation of the obtained

data, so the data processing is controllable.

Two centers: 2 clinical trial institutions were selected to carry out the clinical trial. A higher number of cases can be obtained in the same amount of time than a single-center trial, so the clinical trial time can be shortened.

Single-group target value method: Because the same device for investigational medical devices is radioactive and difficult to obtain, the existing treatment methods are not feasible due to objective conditions, so the single-group target value method is used. Moreover, the applicable population and main evaluation indicators of experimental medical devices can be fully defined and relatively stable, and the main evaluation indicators adopt the effective rate mentioned in the "Guiding Principles for the Technical Review of Clinical Evaluation of Proton Carbon Ion Therapy Systems" (Circular No. 4 of 2018 of the State Food and Drug Administration), which is relatively objective and reproducible. According to the Guidelines for the Technical Review of Clinical Evaluation of Proton Carbon Therapy Systems, the target therapeutic rate of investigational medical devices should be at least 80%, and the expected value is 95%. Among them, the effective definition is: CR+PR+SD (complete response CR, partial response PR, and stable disease SD), which is basically consistent with the definition of tumor disease control rate in this clinical trial. Therefore, no control group was set up in this clinical trial, and a single-group target value method was used to evaluate whether the tumor disease control rate of ProBeam reached the target value (80%), whether the proportion of CTCAE grade 3 toxicity, the main safety evaluation index, was lower than the acceptable value (5%), and whether the proportion of CTCAE grade 4 and 5 toxicity was acceptable (0%).

1.3 Statistical assumptions

In this study, a single-group target-value experimental design was adopted, and the hypothesis test was as follows:

H0: $\pi_1 \leq \pi_0$; *H1*: $\pi_1 > \pi_0$

Test level α = 0.05 (two-sided).

Among them, the disease $\pi_1\pi_0$control rate and its target value of the ProBeam Proton Therapy System for radiation therapy in cancer patients are respectively.

1.4 Number of subjects

This clinical trial intends to enroll 47 subjects. The sample size determination process is as follows:

This clinical study is a clinical validation design of a single group of target values, and the main effectiveness indicator tumor disease control rate is the basis for sample size estimation. According to the "Guidelines for the Technical Review of Clinical Evaluation of Proton Carbon Ion Therapy System" (Announcement No. 4 of 2018

of the State Food and Drug Administration), the target value is set at 80%, the bilateral significance level is 0.05, the power is 80%, and the sample size estimation professional software PASS 15.0 is used, and the sample size of the experimental group is at least 42 cases calculated by the above parameters. Considering that about 10% of the cases may be dropped out or lost to follow-up during the clinical validation, the sample size of the experimental group was expanded to 47 cases.

In this trial, the two centers adopted competitive enrollment, and the investigators of the two centers were diagnosed, operated and treated according to the requirements of relevant tumor diagnosis and treatment guidelines, norms and consensus, and it is expected that there will be only a few patients in one center, and the center will have little impact on efficacy and safety, and the center effect will no longer be considered in the analysis.

2 Evaluation indicators

2.1 Effectiveness evaluation indicators

2.1.1 Key Effectiveness Indicators

- **Tumor disease control rate (DCR) at 3 months after the end of last treatment**

The occurrence of CR, PR and SD after the end of treatment was considered to be disease control, and the absence of biochemical recurrence at the end of treatment of prostate cancer was considered to be disease control. Proportion of subjects with disease control 3 months after the end of the last radiation therapy.

Calculation formula: DCR = number of subjects under disease control / total number of subjects × 100%

2.1.2 Secondary effectiveness measures

- **Objective response rate (ORR)**

  CR or PR was considered objective remission at the end of treatment, no biochemical recurrence occurred at the end of prostate cancer at the end of treatment, and no regional lymph node metastasis or distant metastasis was considered objective remission. Proportion of subjects with objective remission at each time point after the end of the last treatment.

  Calculation formula: ORR = number of subjects with objective remission / total number of subjects × 100%

- **Time to Sustained Remission (DOR)**

  The time from the first assessment of the tumor as CR or PR to the first assessment of PD or death from any cause.

  Calculation formula: DOR = time to first assessment of PD or death from any cause - time to first

assessment of CR or PR.

- **Tumor disease control rate (DCR) at 1 month after the end of last treatment**

The occurrence of CR, PR and SD after the end of treatment was considered to be disease control, and the absence of biochemical recurrence at the end of treatment of prostate cancer was considered to be disease control. Proportion of subjects with disease control 1 month after the end of the last treatment.

Calculation formula: DCR = number of subjects under disease control / total number of subjects × 100%

- **Tumor markers (if required)**

Tumor marker examination was performed and clinically significant changes in tumor markers (before and after radiation therapy) were reported at the discretion of the investigator.

- **Tumor-specific symptoms**

Symptoms are recorded according to the type of disease, which may include, but are not limited to, the following: pain, swallowing function, mobility, bleeding, visual acuity, appetite/weight, superficial lymph node size, and clinically significant changes in reported symptoms (before and after radiation therapy) as judged by the investigator.

- **Ease of use (ProBeam System, Radiation Therapy Management Software (OIS), Radiation Therapy Planning Software (Eclipse))**

Investigators using the corresponding functions scored according to the Likert scale and collected open-ended questions to evaluate the comprehensive feeling of ease of use during the treatment.

2.2 Safety evaluation index

2.2.1 Key safety indicators

- **Proportion of CTCAE grade 3 toxicity**

Proportion of subjects with grade 3 toxicity in the trial cycle.

Calculation formula: Proportion of CTCAE grade 3 toxicity = number of subjects with CTCAE grade 3 toxicity in the test cycle / total number of subjects ×100%;

- **Proportion of CTCAE grade 4 and 5 toxicity**

Proportion of participants with grade 4 and 5 toxicity during the trial cycle.

Calculation formula: Proportion of CTCAE grade 4 and 5 toxicity = number of subjects with CTCAE grade 4 and 5 reactions in the trial cycle / total number of subjects × 100%;

2.2.2 Secondary safety metrics

- **Proportion of CTCAE grade 1 and grade 2 toxicity**

Proportion of participants with Grade 1 and Grade 2 toxicity in the trial cycle.

Calculation formula: Proportion of CTCAE grade 1 and grade 2 toxicities = number of subjects with CTCAE grade 1 and 2 toxicity in the trial cycle/total number of subjects ×100%;

- **Laboratory tests (blood routine, coagulation routine, urine routine, liver function, renal function)**

Laboratory tests were performed and, in the judgment of the investigator, clinically significant changes in laboratory markers (before and after radiation therapy was administered) were reported.

- **ECOG Grade of Strength Status**

ECOG performance status grading assessment was performed and clinically significant changes in examination results (before and after radiotherapy) were reported at the discretion of the investigator.

- **Tumor recurrence rate**

The ratio of the number of subjects with tumor recurrence to the total number of subjects. Tumor recurrence refers to the growth of a tumour that is clinically controlled after radiotherapy and grows over a period of time, and is of the same nature as the primary tumor. Recurrence referred to clinically mostly refers to local recurrence, such as recurrence of residual organs, irradiation fields, and adjacent organs affected. Prostate cancer recurrence refers to biochemical recurrence, and PET-CT is required to confirm that the tumor has metastasized to lymph nodes or distant metastases.

Calculation formula: tumor recurrence rate = number of subjects with tumor recurrence / number of total subjects ×100%;

- **Incidence of adverse events**

An adverse event (AE) is an unfavorable medical event that occurs during the course of a clinical trial, whether or not device related.

Calculation formula: incidence of adverse events = number of subjects with adverse events in this group / number of all subjects in this group ×100%;

- **Incidence of serious adverse events**

A Serious Adverse Event (SAE) is a serious adverse event that occurs during a clinical trial that results in death or serious deterioration of health, including fatal illness or injury, permanent defects in body structure or function, hospitalization or prolonged hospital stay, medical or surgical intervention to avoid permanent defects in body structure or function, fetal distress, Fetal death or congenital anomalies, congenital defects and other events.

Calculation formula: incidence of serious adverse events = number of subjects with serious adverse events in this group / number of all subjects in this group ×100%;

- **Incidence of device defects**

Device defects refer to the unreasonable risk that medical devices may endanger human health and life safety under normal use during clinical trials, such as crashes.

Calculation formula: incidence of device defects = number of device defects / number of device use ×100%;

3 Statistical analysis set

The following analysis sets were defined in this trial for statistical analysis.

Full Analysis Set (FAS): According to the basic principles of intention-to-treat analysis, all participants who received at least one treatment with an investigational device and at least one post-baseline observational data will be included in the FAS. FAS will be used as the main population for the baseline data and effectiveness evaluation sensitivity analysis of this study. Exclusion is only possible in very limited circumstances, including cases where important enrollment criteria have been violated and no observational data have been available after enrollment.

Per-Protocol Set (PPS): is a subset of FAS and refers to subjects with measurable lesions at baseline who have completed at least one primary efficacy measure assessment after baseline. PPS will be the main population in the evaluation of the effectiveness of this study.

Safety Set (SS): All participants who received at least one treatment with an investigational device and had at least one safety evaluation. SS will be the primary population for safety analysis in this study.

The baseline characteristics will be assessed using the full analysis set, the effectiveness will be assessed using both the full analysis set and the conformance set, and the safety analysis will use the safety dataset.

4 data processing

4.1 Processing of data from unscheduled visits

The processing of unscheduled event data is agreed as follows:

In addition to the scheduled visit data, unscheduled event data should also be considered when judging the baseline value. Unless otherwise specified, the last non-missing test value before the first treatment is used as the baseline value.

Safety trial (e.g., laboratory tests, vital signs) metrics aggregated by visit, and only scheduled visit test results are summarized.

When performing the worst observational data carry-over and fill (WOCF) analysis for the main effectiveness evaluation indicators, the unplanned event data will be considered in addition to the planned visit data, but only the planned visit data will be descriptively summarized.

All unscheduled event data should be tabulated.

Unless otherwise specified, the data of unscheduled visits will be summarized and tabulated according to the above principles, otherwise they will be described in a footnote under the statistical analysis table.

4.2 Handling of missing dates for various events

For various events (previous/concomitant medications, concomitant treatments, AEs, etc.), according to the definition and nature of different events, the fill-in rules for the absence of their start/end dates are agreed. If the end date of each event is missing, it will not be filled, and the rules for missing the start date are shown in Table 2.

Table 2 Incomplete filling rules with start dates

Missing values	Fill the rules
day	If the year and month are the same as the year and month of the treatment start date, and the end date is after the treatment start date or is missing, the treatment start date is used to fill in; Otherwise fill for 1 day.
Day/Month	If the year is the same as the treatment start date, and the end date is after the treatment start date or is missing, the treatment start date is used to fill in; Otherwise fill for January 1.
Day/Month/ Year	If the end date is after the treatment start date or is missing, the treatment start date is used to fill in; Otherwise, no filling will be carried out.

4.3 Effectiveness indicators are missing

When analysing the main effectiveness evaluation indicators based on PPS, it is not necessary to consider filling them.

In the sensitivity analysis of the main effectiveness evaluation indicators based on FAS, the missing values of the main effectiveness evaluation indicators were not filled.

The missing values of qualitative secondary effectiveness evaluation indicators ORR and DCR were filled by the method of worst observational data carryover (WOCF).

The missing value of the quantitative secondary effectiveness evaluation index DOR was not filled.

Other secondary effectiveness evaluation indicators, such as tumor markers, tumor-specific symptoms, and

product ease of use, were not filled.

4.4 Handling of missing safety indicators

The missing values of safety evaluation indicators were filled by the method of Worst Observational Data Carryover (WOCF).

According to the conservative principle, if the severity of an AE is missing, it will be recorded as "grade 3" in the summary description, and if the relationship between an AE and the investigational medical device is missing, it will be recorded as "probable" in the summary description as "probable".

4.5 Missing processing of other data

If other data are missing, a footnote will be provided under the statistical analysis table if there is a special note to fill in the summary.

5 Methods of statistical analysis

5.1 Statistical software

Statistical Analysis System (SAS) version 9.4 was used for programmatic analysis.

5.2 General principles

In general, continuous variables will be statistically described using the number of cases, arithmetic mean, standard deviation, median, 25% quantile (Q1), 75% quantile (Q3), minimum and maximum values, etc., while categorical variables will be statistically described using frequency, frequency, incidence, and composition ratio. Unless otherwise specified, all statistical tests will be performed using a two-sided test of α=0.05 to calculate a two-sided 95% confidence interval.

Unless otherwise specified, the following conventions will be followed for the retention of decimal places in this statistical analysis:

Table 3 Data decimal place retention provisions

Statistics	Decimal place provisions
Arithmetic mean, median, Q1, Q3	1 decimal place more than the actual number of decimal places.
standard deviation	1 decimal place more than the arithmetic mean and no more than 4 decimal places.
Minimum, maximum	Same as the actual number of decimal places.
Frequency, incidence, composition ratio	Keep 1 decimal place as a percentage, and the result with a frequency of 0 is "0", and the result is 100% of the display is "100".
Confidence limit	Metrological data: Same as arithmetic mean decimal places

	Counting data: 1 decimal place is kept as a percentage.
Test statistics (e.g., chi-square or *t-value, etc.)*.	Keep 4 decimal places.
P-value	Keep 4 decimal places, and if the specific value is less than 0.0001, it will be represented as "<0.0001".

5.3 Subject characteristics

5.3.1 Distribution of participants

The number and percentage of subjects participating in screening, screening success, enrollment, completion of radiotherapy, completion of primary efficacy evaluation, completion of trial and early withdrawal, and each reason for withdrawal will be described throughout the trial.

5.3.2 Deviation from the protocol

Depending on protocol deviations and the specific situation, participants who are not included in FAS, PPS, or SS will be discussed at the data review meeting and identified prior to database locking.

The number, number and incidence of protocol deviations in each category are summarized and the list details the regimen deviations of the subjects.

5.3.3 Demographic characteristics and baseline data

Demographic data and baseline data will be analysed based on FAS. The demographic indicators included gender and age, and the baseline data indicators included height, weight, vital signs, ECOG physical condition classification, and cardiac function classification, and the above indicators were summarized descriptively.

5.3.4 History of tumor treatment

The history of tumor treatment will be analyzed based on SS. Treatment history includes surgical treatment history, radiation therapy history, interventional therapy history, cytotoxic drug treatment history, immunotherapy history, and targeted therapy history, and the above treatment history is summarized descriptively.

5.3.5 History of present tumor presentness

The history of present tumor will be summarized based on FAS. The indicators of present history of tumor include diagnosis basis, tumor type, tumor location, tumor status, pathological classification, and TNM stage. The frequency and composition ratio of the above categorical variables were calculated.

The list details the subject's present medical history.

5.3.6 Past medical history

A detailed description of the subject's past medical history was based on the SS list.

5.3.7 Prior/concomitant medications

Prior medication refers to medication taken prior to the first radiation therapy.

Prior/concomitant medications will be summarized based on SS. Prior/concomitant medications were coded using the World Health Organization Pharmacological Dictionary (WHODD) (version: 09/2021) according to pharmacology/therapeutics (ATC02).and Preferred Name (PN) classification, and the frequency and percentage of previous/concomitant medications were counted.

The list details the subject's previous/concomitant medications.

5.3.8 Concomitant therapy

A detailed description of the subject's concomitant treatment based on the FAS list.

5.3.9 Radiation therapy plan

Based on FAS, the radiotherapy plan was described and summarized, including the treatment cycle, the total dose of the target area of the radiotherapy plan, and the fractional dose. The list describes the radiotherapy plan design for each subject.

The list describes the dose limits for organs at risk.

To summarize the use of respiratory gating by participants in radiotherapy delivery.

5.4 Effectiveness evaluation indicators

5.4.1 Key Effectiveness Indicators

The primary effectiveness evaluation was based on the Full Analysis Set (FAS) and the Protocol-Consistent Set (PPS).

The number and percentage of cases that achieved tumor disease control at 3 months during the follow-up period were calculated, and the 95% confidence interval of tumor disease control rate was calculated by Clopper-Pearson, and the target value of tumor local control rate was 80%, and if the lower limit of the 95% confidence interval of the test results was greater than 80%, the tumor local control rate was reached. The single-sample chi-square test was used to compare whether there was a statistical difference between the local control rate and the target value.

For the evaluation results of the imaging review team, if the efficacy evaluation results of the two evaluators are consistent, the final evaluation results of the two evaluators will be taken, and if the evaluation results of the two evaluations are inconsistent, the independent evaluation value of the third evaluator will be taken as the final evaluation results.

Based on FAS, the sensitivity analysis of the main effectiveness indicators was carried out, and the missing values of the main effectiveness evaluation indicators were filled by the method of Worst Observational Data

Carryover (WOCF).

5.4.2 Secondary effectiveness measures

Secondary effectiveness assessments were based on the full analysis set (FAS) and the permissible set (PPS).

- Objective response rate (ORR)
- Time to Sustained Remission (DOR)
- Tumor disease control rate (DCR) at 1 month during follow-up period
- Tumor markers (if required)
- Tumor-specific symptoms
- Ease of use (ProBeam System, Oncology Information System (OIS), Treatment Planning System (Eclipse))

The 95% confidence interval was calculated by Clopper-Pearson for the above secondary efficacy indicators of "objective response rate (ORR)" and "tumor disease control rate (DCR) during the follow-up period of 1 month".

For the "time to sustained response (DOR)" secondary efficacy measure, describe the sustained response.

Descriptive statistics were performed on the percentage of measurable tumor longest diameter sum (SLD) from baseline, and a waterfall chart was made for the maximum percentage reduction of SLD in each subject compared with the screening period.

For the secondary efficacy indicators of "tumor markers" and "tumor-specific symptoms", the changes before and after are described, and the changes are described in the table.

For the secondary efficacy index of "product ease of use", the scores of each category and the total score were calculated, and the details of the open questions were described in a table.

5.5 Safety evaluation index

The safety metrics are based on the Safety Dataset (SS).

The main safety indicators included the proportion of CTCAE grade 3 toxicity and the proportion of CTCAE grade 4 and 5 toxicity.

Secondary safety measures included the proportion of CTCAE grade 1 and 2 toxicity, laboratory tests, ECOG performance status classification, tumor recurrence rate, adverse events, serious adverse events, and device defects.

5.5.1 Proportion of CTCAE toxicity

The severity of AEs was assessed according to Common Adverse Event Common Terminology Criteria

(CTCAE) V5.0.

Grade 1: mild, asymptomatic or mildly symptomatic, clinical or diagnostic findings only, no treatment required;

Level 2: moderate, minimal, localized, or non-invasive interventions, age-related limitations in instrumental activities of daily living (ADLs) (instrumental ADLs refer to cooking, grocery or clothing shopping, phone access, financial management, etc.);

Grade 3: severe or medically significant, but not immediately life-threatening, hospitalization or prolonged hospital stay, disability, restriction of self-care ADL (self-care ADL refers to bathing, dressing and undressing, eating, toileting, taking medications, not being bedridden);

Grade 4: life-threatening; requiring urgent intervention;

Grade 5: AE-related death.

The number and percentage of subjects who achieved each grade of CTCAE toxicity were calculated, and the details of toxicity were described in a table.

5.5.2 Laboratory tests

The results of laboratory indicators (blood routine, coagulation routine, urine routine, blood biochemistry) and their changes from baseline were summarized and described at each planned visit, the changes before and after treatment were evaluated, and the pre- and post-treatment cross-over tables of clinical evaluation (normal, abnormal and clinically significant) were given.

5.5.3 ECOG Grade of Strength Status

Summarize and describe the ECOG physical status classification for each program visit.

5.5.4 Tumor recurrence rate

The number and percentage of subjects with tumor recurrence were calculated.

5.5.5 Adverse events

The incidence, occurrence and severity of adverse events and serious adverse events were summarized by descriptive statistics and MedDRA (V25.0) medical terminology according to system organ classification.

(1) The number (incidence) and number of AEs of various types of AEs are summarized and described, including all AEs, TEAEs, TEAEs related to investigational medical devices, SAEs, and SAEs related to investigational medical devices.

Treatment Emergent Adverse Event (TEAEs) are defined as unfavorable medical events occurring between the start of proton therapy in clinical study subjects and the end of the trial, regardless of

whether they are treatment related.

Definition of Treatment-Period Adverse Events Related to Investigational Medical Devices: Treatment-period adverse events that are "definitely related", "probably related", "probably related" to the investigational medical device.

(2) For the types of AEs described in (1), the number of occurrences (incidence) and the number of cases of each classification are described based on the classification of system organ classification (SOC) and preferred term (PT).

(3) For the types of AEs described in (1), the number of occurrences (incidence) and cases of different severity of each classification are described based on the classification and severity of the system organ classification (SOC) and preferred term (PT).

(4) A list of AEs, TEAEs, TEAEs related to investigational medical devices, SAEs, and SAEs related to investigational medical devices is listed, including but not limited to the name of adverse events, severity, relationship to trial operation, AE start date and end date, etc.

5.5.6 Device defects

Calculate the number of device defects, the number of cases and the incidence rate, and describe the specific situation of the device defects in detail, including but not limited to the description of the device defect, the date of occurrence, the treatment results, etc.

5.6 Sensitivity analysis

If the receiver effectiveness index was filled by the worst observational data carry-over (WOCF) method, the sensitivity analysis of the main effectiveness measure was performed based on FAS. When the conclusions of FAS and PPS are consistent, the confidence of the test results can be enhanced. When the conclusions of the two groups are inconsistent, the analysis based on the inclusion of PPS population should be the main one, and the differences should be fully discussed and explained.

5.7 Subgroup analysis

Subgroup analyses were performed for primary effectiveness measures, including but not limited to:

(1) Tumor site (tumors of the nervous system, head and neck, chest, abdomen, spine, pelvis, limbs, etc.);

The number and percentage of local control of tumors under the planned visits of each subgroup were summarized.

5.8 Interim analysis

Not applicable.

6 Changes to the protocol analysis plan

Section 8.7.2 of the original protocol provided that the missing value of the safety index was estimated using the worst-case scenario. According to the conservative principle, SAP has made the following conventions: if the severity of an AE is missing, it will be recorded as "level 3" in the summary description, and if the relationship between a TEAE and the investigational medical device is missing, it will be recorded as "probable" related to the investigational medical device in the summary description.

7 Annex

Appendix 1 Flowchart of Subject Distribution

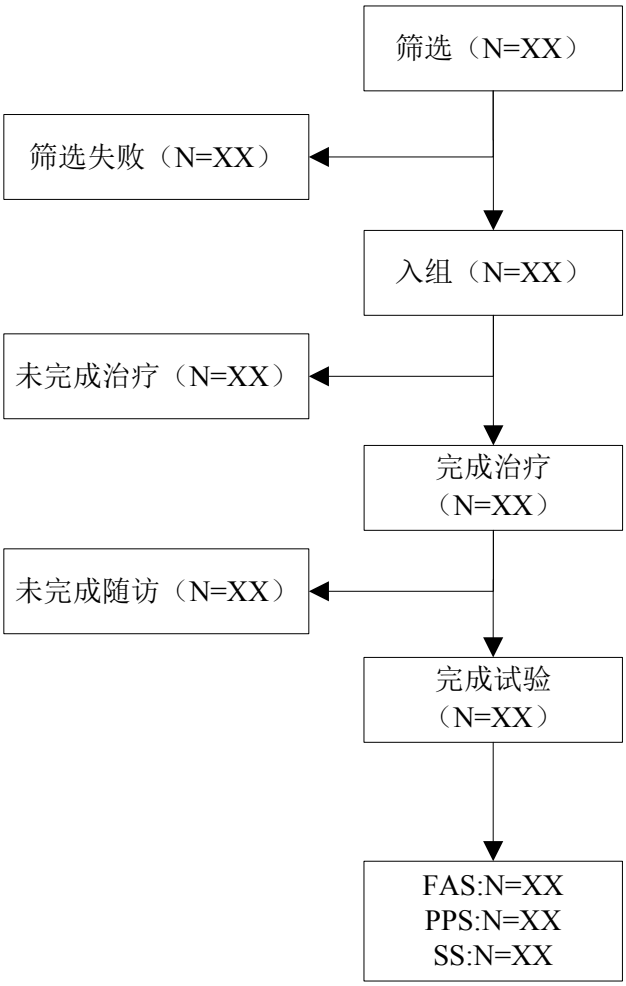

Fig.1 Sample flow chart of subject distribution