Clinical Trial Protocol for a Novel Localization Device versus Hookwire for Thoracoscopic Resection of Small Pulmonary Nodules

Name of the investigational medical device: Disposable pulmonary nodule localization needle

Model & specification: SS510-10

Registration number: ChiCTR1900027346

Registration name: A randomized controlled study for the clinical application of a new type of positioning needle and hook wire positioning needle

Protocol version: 1.0

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Contents

1 BACKGROUND

With the development of the thin-slice and high-resolution computed tomography (CT) and the improvement of people's health consciousness in recent years, more and more small pulmonary nodules (SPNs) have been discovered during routine medical tests[1]. However, the property of the SPNs can hardly be identified only through imaging examination. Accurate pathological diagnosis is essential.

The CT-guided percutaneous needle biopsy of lung and the bronchoscopy biopsy are common means adopted to obtain the histological features of SPNs, but their accuracies are influenced by various factors of the nodules[2]. Therefore, minimally invasive surgery is required to obtain the pathological result of the nodule. In recent years, video-assisted thoracoscopic surgery (VATS) provides effective technical support for the early diagnosis and treatment of pulmonary nodules. However, some pulmonary nodules are too small or too deep to be reached. Therefore, localization and sampling of pulmonary nodules are difficult in some cases. The literature reported that the rate of conversion to thoracotomy was up to 46% due to insufficient localization of pulmonary nodules[3]. Therefore, localization methods for SPNs were invented to solve the problem.

At present, many techniques can be used for pulmonary nodule localization. Representatives include dyeing localization, intraoperative ultrasonic localization, lipiodol, and hookwire, etc. Each method has its own disadvantages. The dyeing localization technique is rarely adopted due to its high incidence rate of complications[4]. As for intraoperative ultrasonic localization, accurate localization can hardly be achieved due to the existence of pulmonary alveoli, and largely depends on the experience of the operator[5]. The lipiodol labeling technique requires finger palpation to find the nodule and may result in lung tissue damage[6]. The indication approved by the Chinese Food and Drug Agency (CFDA) of the hookwire is for breast tumor localization. However, many doctors worldwide have performed clinical studies on using the hookwire for SPNs localization and reported good results in the literature, which indicated that hookwire is a convenient localization method for SPNs with high accuracy[2,7,8]. However, according to some literature, hookwire also has many complications[7,9,10]. Therefore, a more safe and effective localization technique is needed.

We have recently developed a new device that has a four-hook anchor with scaled sutures, and demonstrated a high success rate, good tolerance of patients, and low rate of complications for preoperative localization of

SPNs in a multi-center clinical trial[11]. However, the effectiveness and safety between the new device and hookwire are still unclear. Here we conduct a randomized clinical trial to compare the two localization devices.

2. EXPERIMENTAL PRODUCT CHARACTERISTICS, MECHANISMS AND TRIAL SCOPE

2.1 Product Characteristics

The disposable pulmonary nodule localization needle is mainly comprised of a puncture needle, a pushing tube, an anchor claw, a suture and a protective tube. The puncture needle is comprised of a needle tube, a handle and a buckle. The distal end of the suture is connected to the anchor claw. The proximal end of the suture is inside the pushing tube. The suture is divided into three parts by three colors. Relevant structures are shown in **Figure 1**.

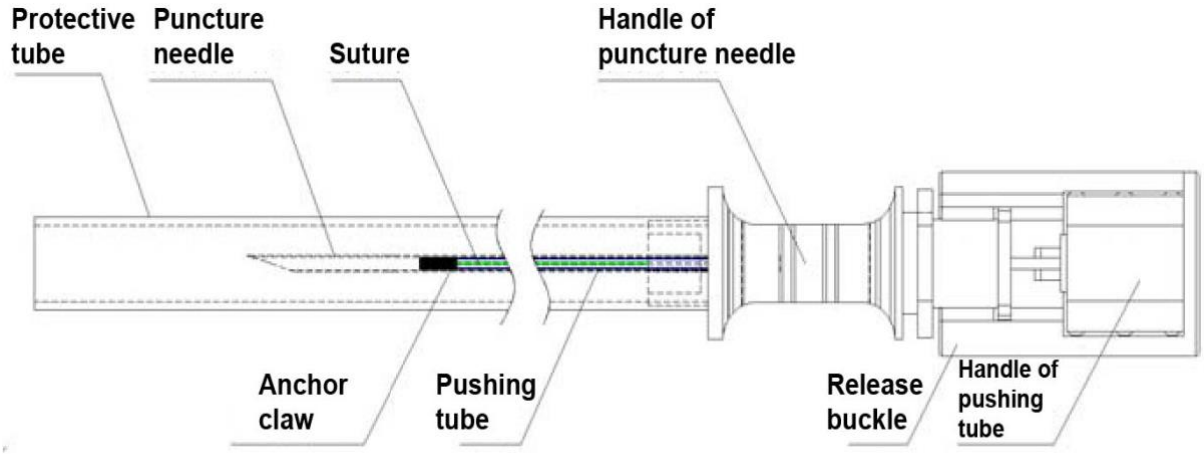

Figure 1 The structure of the novel localization device.

2.2 Product Mechanisms

The disposable pulmonary nodule localization needle is mainly comprised of a puncture needle, a pushing tube, an anchor claw, a suture and a protective tube. Guided by CT, the puncture needle inserts through the chest wall and the lung, and reaches the edge of the pulmonary nodule. Then the pushing system releases the anchor claw which hooks up the pulmonary tissue. In the resection surgery later, the scale on the suture can be used for estimating the depth.

2.3 Trial Scope

Patients who accept the surgery for pulmonary nodule localization.

3 EXPERIMENTAL PRODUCT INDICATION

Pulmonary nodule localization.

4 CONTENTS AND OBJECTIVES OF THE TRIAL

4.1 Trial Contents

The trial is performed to evaluate the safety and efficacy of a novel disposable pulmonary nodule localization needle produced by Ningbo Senscure Biotechnology Co., Ltd versus hookwire which is a classic disposable pulmonary nodule localization needle. About 409 patients who are suitable for pulmonary nodule resection by surgery are enrolled according to the inclusion/exclusion criteria of the trial. Localization is performed using the pulmonary nodule localization needle under the guidance of CT before the resection. Then the pulmonary nodule is resected by VATS. The successful localization rate, adverse events (mainly refer to complications of localization), the pain scoring and the localization time during the trial are calculated and compared.

4.2 Trial Objectives

Evaluate and compare the safety and efficacy of the novel localization device versus hookwire for thoracoscopic resection of SPNs.

● **Primary objective**

Evaluate and compare the successful localization probability of the novel localization device and hookwire for pulmonary nodules.

● **Secondary objective**

Evaluate and compare the adverse events probability, the localization time, and the pain degree of the novel localization device and hookwire.

5 SCOPE OF SUBJECTS

5.1 Inclusion Criteria

(1) 18 years old ≤ Age ≤ 80 years old, of either sex;

(2) Patients who are confirmed to have pulmonary nodules (diameter ≤1 cm, solid or ground-glass nodules) by chest CT examination and expected to receive wedge resection or segmentectomy of the lung by VATS;

(3) Significantly enlarged lung hilus or mediastinal lymph node is not observed by CT examination of the chest;

(4) Performance status (PS): PS scale under 3;

(5) Patients who voluntarily participate in and sign the informed consent form (ICF).

5.2 Exclusion criteria

(1) Patients who are not suitable for localization before surgery based on the judgment of the investigator, e.g., patients who have pleural effusion or severely damaged lung tissue;

(2) Systemic factors: sepsis, repeated pulmonary infection, any type of severe infectious diseases 1 month before surgery;

(3) Patients having severe diseases of heart, brain, lung, liver and kidney or severe hypertension;

(4) Patients having severe coagulation disorders;

(5) Patients having any distant metastasis;

(6) Patients who participate in the clinical trial of other drugs or medical devices within 30 days before screening;

(7) Other conditions which are considered as inappropriate for this clinical trial.

6 CLINICAL EVALUATION CRITERIA

6.1 Evaluation Criteria of Efficacy

● **Successful localization rate**

Successful localization is defined as: the localization device is released and located in or around the nodule (within 10 mm to the edge of the nodule), and no dislodgement of the device occurred from the localization procedure to the first exploration of VATS. Moreover, no fault or fracture of the device is observed during the whole procedure.

If the localization needle should be changed during the study (for single or multiple nodules), the change information must be recorded. Localization evaluation is performed for all the used products. For multiple nodules (using multiple localization needles), localization is considered as a failure if the localization of one site fails.

6.2 Evaluation Criteria of Safety

Adverse events during the trial mainly refer to complications of localization caused by percutaneous lung puncture, mainly including:

● Pneumothorax: Air enters into the pleural cavity due to puncture and results in pneumatosis. Evaluation method: CT examination is performed before the end of localization to find whether there is any extremely

low-density air shadow in the pleural cavity near the puncture needle and whether lung tissue is compressed and shrunk to varying degrees. Pneumothorax is classified into small pneumothorax (＜20%), medium pneumothorax (20%–40%) and large pneumothorax (＞40%) according to the collapse degree of the lung. Pneumothorax caused by puncture generally belongs to small pneumothorax and does not require any special treatment.

● Hemorrhage: refer to pulmonary bleeding caused by a puncture. Evaluation method: CT examination is performed before the end of localization to find whether there is any diffuse or nodular shadow over the tissue around the puncture site. Bleeding exists if yes. Bleeding caused by puncture is generally shown as a flaky, cloud- or cotton-shaped effusion shadow or the effusion shadow along the needle passage. No special treatment is needed because the bleeding amount is small.

● Pleural reaction: Pleural reaction refers to a series of reactions in the process of a pleural puncture due to the diagnosis or treatment of thoracic diseases, such as cough, dizziness, chest tightness, pale complexion, sweating and even fainting. In case of pleural reaction, stop the puncture immediately, put the patient in a supine position, keep the patient warm, and observe the changes of pulse, blood pressure and consciousness. Those with mild symptoms can relieve themselves after rest. For patients with obvious sweating and low blood pressure, oxygen inhalation and 10% glucose supplement of 500 ml were given. If necessary, inject adrenaline subcutaneously to prevent shock.

6.3 Evaluation Criteria of Usability

The following indexes are used to evaluate the usability of the localization needle:

● Localization: Pushing ability, penetration ability, ease of use, withdrawal performance and successful release or not, etc.

● Nodule resection: whether the suture is detectable and fractured, and whether the anchor claw shifts and unhooks, etc.

When more than one localization needles are used for a single lesion, the poorest performance evaluation is recorded.

7 OVERALL DESIGN OF THE TRIAL

7.1 Trial Design

This randomized clinical trial is designed as a parallel, prospective, open-label study. The intervention group is the novel localization device, and the control group is hookwire which is a classic localization device. The

study area is located in the Department of Thoracic Surgery of Shanghai Chest Hospital.

● **Primary endpoint**

The localization success probability of the novel localization device and hookwire for pulmonary nodules.

● **Secondary endpoints**

(1) The probability of pneumothorax, hemorrhage, the pleural reaction of the novel localization device and hookwire;

(2) The pain degree caused by the novel localization device and hookwire, measured by the visual analog scale (VAS);

(3) The time required for the localization procedure of the novel localization device and hookwire.

7.2 Randomization Methods

We use the Stata 14 software (StataCorp, Texas, USA) to produce the randomization number, which will be allocated to the patients signed the informed consent by our investigators. According to the number, the patients are randomized allocated into the different study groups. Both the surgeons, the radiologists, and the patients were masked as to the allocation schedule. Sealed and numbered envelopes that contained the allocated group for each patient were prepared and opened at the beginning of each localization procedure.

7.3 Investigational Product

Product name: Disposable pulmonary nodule localization needle

Manufacturer: Ningbo Senscure Biotechnology Co., Ltd.

Product specifications & model: SS510-10

7.4 Number of Cases

At least 409 cases.

7.5 Trial Process

This trial includes the following periods: (see **Table 1**)

(1) Case screening;

(2) Case enrollment;

(3) Localization;

(4) Surgery.

Table 1 The detail periods and recording items of the clinical trial.

Item	Screening period	Localization	Surgery

Times of visit	**V1**	**V2**	**V3**
Number of days	**-7-0 day**	**0 day**	
Sign the ICF	×		
Inclusion/exclusion criteria	×		
History	×		
Demographic data	×		
Physical examination	×		
Vital signs	×	×	×
CT	×	×	
AE record	×	×	×

Remarks: Vital signs: Blood pressure, heart rate, respiration, pulse and chest examination, etc.

7.6 Localization Methods

CT-guided localization is arranged before pulmonary nodule resection. Firstly, chest CT scanning is performed. Guided by CT image, the operator selects the appropriate position and puncture site and determines the best insertion angle and path. After local anesthesia, the localization device is used. The usage is as follows:

(1) Open the inner package, take out the localization needle, and remove the protective tube;

(2) Confirm the position of the pulmonary nodule through CT image, and insert the localization needle into the chest wall and lung to reach the edge of the pulmonary nodule under CT guidance;

(3) Remove the release buckle from the localization needle, push the pushing tube to the bottom, so as to release the anchor claw from the needle tube. The anchor claw will be located around the nodule (within 10 mm to the edge of the nodule);

(4) Withdraw the puncture needle from the pulmonary nodule edge to the pleural cavity;

(5) Completely pull the pushing tube out of the localization needle, then put the pushing tube back to the localization needle, and push the pushing tube to the bottom, so that the proximal end of the suture is pushed into the chest wall;

(6) Remove the localization device, press on the puncture point with sterile gauze to stop any possible bleeding, and send the patient to the operating room.

7.7 Measures to Reduce and Avoid Bias

Training for investigators: Before the clinical trial, the investigators are trained by the protocol and are told how to use the experimental product, so that investigators can familiarize themselves with the investigational product and find new product-related information during the clinical trial.

Monitoring for the trial: The monitor appointed by the sponsor will regularly monitor the trial hospital on site, to guarantee that the study protocol is strictly abided by. The monitor will also check the original data to ensure their consistency with those in the case report form (CRF).

Additionally, if the patients' baseline information (age, gender, lesion location) between two groups aren't balanced, we will use the propensity score method (PSM) to match this information.

7.8 Standards and Procedures for Discontinuing Trial/Treatment

● Trial discontinuation:

(1) A huge error of the clinical verification protocol is found during the trial, and the product effectiveness can hardly be evaluated;

(2) The sponsor or CFDA requires to terminate the trial.

● Treatment discontinuation:

(1) Withdrawal due to the subject's reason:

- ◆ The subject does not comply with the verification plan;
- ◆ Other reason of the subject.

(2) Withdrawal due to medical reasons:

- ◆ Poor protocol compliance;
- ◆ Serious adverse events (SAEs);
- ◆ Serious complication.

● Procedure:

If the trial is discontinued or suspended for any reason, the Principal Investigator (PI)/Clinical Investigation Site should timely notify relevant subjects, fully protect their rights and interests, and ensure that they can receive proper treatment and follow-up. Meanwhile, the PI/Clinical Investigation Site should notify the superior department in charge of medical treatment and public health in accordance with relevant laws,

regulations and management procedures. In addition,

(1) If the PI discontinues or suspends this trial without reaching any agreement with the sponsor in advance, the PI should immediately notify the administrative department for the clinical trial of medical devices in the Clinical Investigation Site, and timely provide a detailed written explanation for discontinuation or suspension to the sponsor and the medical ethics committee.

(2) If the sponsor discontinues or suspends this trial, the PI should immediately notify the administrative department for clinical trial of medical devices in the Clinical Investigation Site, and timely provide detailed written explanation for discontinuation or suspension to the medical ethics committee.

(3) If the medical ethics committee discontinues or suspends its approval for this trial, the PI should notify the administrative department for clinical trial of medical devices in the Clinical Investigation Site, and timely provide a detailed written explanation for discontinuation or suspension to the sponsor.

7.9 Monitoring Plan

Monitoring is to verify that: I. Rights and health of the subject are protected; II. The reported data are accurate, intact and supported by the original document; III. This trial is implemented as per the protocol and conforms to applicable regulations and management procedures for the clinical trial.

Investigator's obligations during monitoring:

(1) Provide completed CRF and relevant data and facilitate monitoring in terms of data traceability conditions, source materials and venues, etc.;

(2) Coordinate relevant personnel to assist the monitoring.

Monitoring process:

(1) Before monitoring, the monitor shall inform the investigator in advance, and notify the office of the Clinical Investigation Site if necessary;

(2) The monitor shall confirm whether the problem found last time has been solved or not in each monitoring;

(3) During monitoring, the monitor shall timely communicate with the investigator with regard to the problem found:

- ◆ The monitor shall fill in the feedback form, and submit it to the investigator, if necessary, to the office of the Clinical Investigation Site;
- ◆ The monitor shall supervise and urge the investigator to solve the found problem;

◆ After the completion of monitoring, the monitor shall prepare the monitoring and visiting report and submit it to the project leader.

Detailed rules and requirements of monitoring shall be subject to internal Standard Operating Procedures of the sponsor and in line with requirements of the administrative department for clinical trial in the Clinical Investigation Site, and comply with relevant national laws and regulations on clinical trials.

8 TRIAL DURATION AND ITS JUSTIFICATION

8.1 Trial Duration

This clinical trial will last about 5 months.

8.2 Justification

Whether the localization is accurate or not can be determined by the CT examination. The localization needle will be removed together with the resected tissue upon resection of pulmonary nodules. Considering relevant literature and endpoint measurements of this trial, the screening and enrollment period is about 3 months. Taking ethical approval and statistical analysis into account, this clinical trial will last about 5 months.

8.3 Enrollment Time

Enrollment of all subjects is expected to take 3 months.

8.4 Expected Duration of Each Subject

The expected duration of each subject is 1 week.

After admission, the investigator informs the patient of the trial, i.e., the informed consent process. The patient signs the ICF. The investigator screens the patient strictly as per inclusion & exclusion criteria of the protocol. The qualified patient will receive nodule resection surgery. Localization using the investigational medical device will be performed before surgery. Whether the localization is accurate or not can be determined by CT examination upon puncture (the endpoint measurement of effectiveness is the successful localization rate). The nodule resection surgery will be conducted immediately after localization. The localization needle will be removed together with the resected tissue in the surgery. Usability and safety of the device are also observed in the process. The duration is about 1 week.

9 PROBABILITY ANALYSIS OF SUCCESS AND FAILURE

9.1 Probability analysis of success

This clinical trial complies with relevant laws and regulations, including *Good Clinical Practice* and

Declaration of Helsinki, as well as requirements of the trial protocol. This protocol can be implemented only after having been approved by the ethics committee.

Signing the ICF before the trial guarantees the compliance of the subject. Objective indexes are used in the trial, endeavoring to avoid selection bias and information bias; the investigator strictly complies with inclusion criteria, to reduce any possible interference factor.

To sum up, this clinical trial is very likely to be successful.

9.2 Probability Analysis of Failure

Failure of this trial may be caused by any problem of the investigational product, that the investigator fails to strictly execute the clinical protocol, operate and measure as per the specification, and that the drop-out/rejection rate is greater than 10 %, etc. However, these factors will be controlled within the acceptable range. Therefore, this clinical trial is very unlikely to be failing.

10 PREDICTED SIDE EFFECTS AND COUNTERMEASURES

10.1 Adverse Events

10.1.1 Definition of adverse events

● An adverse event (AE) is any adverse medical event that occurred to a clinical investigation subject after receiving the investigational medical device and which does not necessarily have a causal relationship with this treatment.

● All AEs occurred during the trial must be faithfully recorded in the AE form. The investigator shall provide pointed treatment for the AE and follow up until the disappearance or stability of the symptom.

10.1.2 Severity of adverse events

● Mild: Not influence daily activities;

● Moderate: Influence daily activities;

● Severe: Lose the ability of daily activities.

10.1.3 Relationship between adverse events and the investigational product or surgery

The investigator assesses the relationship between adverse events and the investigational product or surgery according to the following criteria:

(1) Relationship to the investigational medical device:

- Certainly related: The reaction is a known reaction type of the suspected product;
- Possibly related: The reaction is a known reaction type of the suspected product; but this reaction may

also be caused by clinical conditions of the patient or other treatment methods;

● Unlikely related: The reaction is not a known reaction type of the suspected product; this reaction may be caused by clinical conditions of the patient or other treatment methods;

● Unrelated: The reaction is not a known reaction type of the suspected product; this reaction may be caused by clinical conditions of the patient or other treatment methods; The reaction disappears when the condition improves or other treatment methods cease. The reaction appears again when other treatment methods are reused;

● Undeterminable: The reaction is similar to a known reaction type of the suspected product; Meanwhile, the same reaction may be caused by other treatment methods.

(2) Relationship to surgery:

● Certainly related: The reaction is a known reaction type of the surgery;

● Possibly related: The reaction is a known reaction type of the surgery; but this reaction may also be caused by clinical conditions of the patient or other treatment methods;

● Unlikely related: The reaction is not a known reaction type of the surgery; but this reaction may also be caused by clinical conditions of the patient or other treatment methods;

● Unrelated: The reaction is not a known reaction type of the surgery; this reaction may be caused by clinical conditions of the patient or other treatment methods; The reaction disappears when the condition improves or other treatment methods cease. The reaction appears again when other treatment methods are reused;

● Undeterminable: The reaction is similar to a known reaction type of the surgery; Meanwhile, the same reaction may be caused by other treatment methods.

10.2 Serious Adverse Events

10.2.1 Definition of serious adverse events

A SAE is defined as any adverse event occurred during the clinical trial that results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in disability/incapacity, influences working competence, and may have caused a congenital anomaly, etc. Although the outcome is not death, life-threatening or hospitalization, some medical events shall also be considered as SAEs if appropriate medical judgment indicates that they may do harm to the subject or require drugs or surgery to avoid the above-mentioned conditions.

10.2.2 Handling and reporting of serious adverse events

In case of any SAE in the trial, regardless of its relationship to the investigational medical device, the investigator shall immediately adopt appropriate treatment and cure measures to the subject and record it in the CRF. Meanwhile, the investigator shall assist the sponsor in reporting the SAE to the PI of the driver unit, the ethics committee, the medical device supervision division of national/local food and drug administration, and the local competent administrative department for health if necessary, within 24 hours after having learned of the SAE. The investigator must carefully fill in the SAE report form item by item, sign and date on the report.

11 STATISTICAL METHODS

11.1 Statistical Analysis Population

Full Analysis Set (FAS): Refer to the ideal subject set which is as close as possible to the intention-to-treat (ITT) principle. This dataset is obtained through rejecting the least subject from all enrolled subjects using a reasonable method.

Per-Protocol Set (PPS): also known as effective cases, effective samples and evaluable cases. Per-Protocol Set is a subset of subjects in the FAS whose compliance with the protocol is tight enough. The subjects are considered as compliant if they have received treatment, have measurements of primary indexes, and have no major protocol violation, etc.

Safety Analysis Set (SAS): The subject set used for safety and tolerance evaluation. The SAS shall include all subjects who have used this investigational medical device and have at least one safety record.

Here, we will use the FAS to analysis baseline information, and the primary endpoint and secondary endpoint will use the SAS to analysis.

11.2 Justification for Cases

The null hypothesis: the Successful localization probability of the novel localization device isn't higher compared with hookwire.

The alternative hypothesis: the Successful localization probability of the novel localization is higher compared with hookwire.

α refers to type I error, while β refers to type II error. Here we consider α as 0.05, and power(1-β) as 80%.

According to some reference and our previous study[2,7,8,11], we consider the Successful localization probability of hookwire as 89% and the Successful localization probability of the novel localization device as 97%, with

one side and the ratio of 2 between control group and intervention group.

We use PASS 11 with Fisher's exact test to calculate the sample size, getting control group with 116 and intervention group with 232. Taking possible 15% drop-out into account, every group will be enrolled 136 patients in the control group and 273 in the intervention group at least. Here, if we can enroll more patients during enrollment time, the patients could be included in our study. This clinical trial can be deemed as successful if the successful localization probability of the novel localization and hookwire is different, addition the successful localization probability of the novel localization has statistic significantly higher than the successful localization probability of hookwire ($p < 0.05$).

11.3 Statistical Analysis Method

11.3.1 General principles

The quantitative data of normal distribution was expressed by average and 95% confidence interval, while the quantitative data of abnormal distribution was expressed by median and interquartile range. Categorical variables were described as numbers and percentages. The two-sided Student's t-test (standard normal distribution) or Wilcoxon rank-sum test (non-standard normal distribution) for continuous variables was used to test differences, and Chi-square test or Fisher's exact test (if expected frequency < 5) were applied for categorical variables. The P-value less than 0.05 was considered a statistical difference. All statistical analyses were using SPSS 22 software (IBM Corporation, Chicago, USA).

11.3.2 Case characteristics

Enrollment and completion condition: The enrolled and completed cases and the list of drop-out cases will be provided.

General information and baseline characteristics: Statistical description will be performed for the patient's demographic information and history of other diseases.

Baseline: Baseline is defined as the basic condition of the subject before clinical operation.

11.3.3 Effectiveness evaluation

Successful localization rate: count conditions of successful localization, estimate the success rate.

11.3.4 Safety evaluation

The statistical description will be performed for the condition of each complication. A table will be made to describe the type, severity, frequency and relationship to the investigational medical device of the AE. The incidence rate of AE will be calculated. Study discontinuation due to AEs as well as severe or serious AEs

will be specially described. The statistical description will be performed for the working condition of the system.

11.4 Significance Level and Power of the Trial

Significance level: 0.05; power: 0.8.

11.5 Expected Drop-Out Rate

The maximum drop-out rate is expected to be about 15%.

11.6 Processing Method for Missing, Unused, Wrong and Unreasonable Data

Missing data of this trial will not be filled and be deemed as invalid data.

11.7 Interim Analysis and Sensitivity Analysis

This study has no interim analysis and sensitivity analysis.

11.8 Deviation Reporting Procedures

The original statistical plan should be strictly complied with. Other statistical methods, which are not specified in the protocol, can be used only after having been reviewed and approved by the ethics committee.

12 DATA MANAGEMENT AND TRIAL QUALITY CONTROL

12.1 Data Management

12.1.1 CRF completion and handover

The doctor must complete the CRF for each enroll case. The CRF shall be filled in with the sign pen. All items must be completed. The completed item cannot be altered at will. The correct change steps are: cross out the wrong data with a short line, fill in the correct result above them, sign and date beside them. The investigator must sign on the CRF to show that he/she has checked all data in the CRF and to confirm that all data are true and accurate. After having been reviewed by the Clinical Research Associate (CRA), the first copy of CRF shall be submitted to the data manager for subsequent data entry and management.

12.1.2 Data entry and modification

A separate data management unit is responsible for data entry and management. The data entry program, which is composed by the data manager using corresponding software, will be used for data entry and management. To guarantee the accuracy of data, two data managers enter and check data separately. In case of any question about the CRF, the data manager will inquire the investigator through the CRA with the Data Request Query (DRQ). The investigator shall reply as soon as possible. The data manager will modify, confirm and enter the data according to the investigator' reply. Another DRQ can be sent if necessary.

12.1.3 Data locking

Although this study is not a blind trial, data review shall meet the requirement of blind review. The PI, sponsor and statistical analyst will lock the data after the data are confirmed to be correct by blind review.

12.2 Quality Control of Clinical Trial

During the study, the CRA appointed by the sponsor will regularly monitor and visit the hospital on site, to guarantee that all contents of the protocol are strictly complied with and that the completed research data are correct. All investigators must pass a unified training and conform to the same recording method and criteria. The whole clinical trial shall be strictly performed. The investigator shall accurately, detailly and carefully fill in the CRF as required, to ensure that the CRF is intact, true and reliable. All observations and findings of the clinical trial shall be verified, to guarantee that data are reliable and that the conclusion of the trial is based on source data. Corresponding data management measures shall be adopted for the stage of clinical trial and data processing.

12.3 Source Materials Saving

Source materials of this trial include the signed ICF, relevant laboratory test reports, case records and other relevant records, etc. which shall be saved in the National Clinical Investigation Site for Drugs of the hospital to which each research center belongs. All source materials and CRFs shall be saved for 10 years after the completion of clinical trial.

12.4 Confidentiality Principles

The investigator shall properly keep all patients' information. All information of patients is de-identified in our dataset. Without the written permission of the investigator, no one can disclose any trial-related data.

13 TRIAL IMPLEMENTATION AND INFORMED CONSENT FORM

13.1 Ethical Requirements

This clinical trial complies with relevant laws and regulations, including *Good Clinical Practice* and *Declaration of Helsinki*, as well as requirements of the trial protocol. This protocol can be implemented only after having been approved by the ethics committee. The PI shall report any modification to the protocol during the trial, SAEs or unexpected AEs which are occurred in the study and may affect the subject's safety to the ethics committee.

13.2 Informed Consent Form

This trial complies with ethics principles of *Declaration of Helsinki* and relevant laws and regulations of China, and will be implemented after having been reviewed and approved by the ethics committee of the Clinical Investigation Site. The ICF can be used only after having been reviewed and approved by the ethics committee.

The patient can fully understand the objective, nature, method, duration, potential benefits and risks, etc. of this trial before participating in the clinical trial. After careful consideration, the patient can voluntarily participate in this trial and sign the ICF before the trial.

The ICF shall be signed jointly by the investigator and the subject. The ICF is in duplicate. The original will be saved by the Clinical Investigation Site, while the copy will be saved by the subject.

13.3 Review and Approval of the Protocol

This trial protocol must be approved by the medical ethics committee. The clinical study report will be submitted to CFDA for the registration of the investigational medical device.

13.4 Protocol Amendment

The investigator must comply with the clinical trial protocol approved by the ethics committee. The ethics committee shall be informed in written of non-material changes which are not related to objectives or endpoints of the clinical trial after protocol amendment. All material amendments to the protocol shall be reviewed and approved by the ethics committee.

13.5 Agreement on Result Publication

Research results may be published or released in scientific sessions. The investigator shall agree to submit the manuscript or abstract to every investigator before submitting for publication. After all investigators allow the publication, and identify no interest conflict, the research could be published. Shanghai Chest Hospital is the owner of the study data.

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Signature Page for the Clinical Investigation Site, the Investigator and the Sponsor

Statement of the Investigator

I agree:

1. Perform this clinical trial strictly following the Declaration of Helsinki, current laws and regulations of China, and requirements of the trial protocol.

2. Accurately record all required data to the CRF and complete the clinical study report on time.

3. Use the investigational product solely for this clinical trial, completely and accurately record the reception and use condition of the investigational product during the clinical trial, and keep records.

4. Receive the monitoring and inspection for this clinical trial by the monitor authorized as well as by the supervision department.

5. Strictly fulfil the clinical trial contract and relevant agreements signed by both parties.

I have read the clinical trial protocol, including the above statement, and I agree with all requirements above.

Opinion of the investigator: Signature: MM/DD/YYYY

Opinion of the Clinical Investigation Site: (seal) MM/DD/YYYY

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