Title

Application of 3D printing technique in small pulmonary nodule localization: A Prospective, Randomized, Controlled, Non-inferiority Trial

Grant

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Principal Investigator

Chang chen

Sponsor

Shanghai Pulmonary Hospital, Tongji university, Shanghai, China

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with Declaration of Helsinki, International Conference on Harmonization guidelines for Good Clinical Practice (ICH E6) and Medical Equipment Specification for the Quality Control of Clinical Trial (State Food and Drug Administration/National Health and Family Planning Commission/Number twenty-fifth). All personnel involved in the conduct of this study have completed human subject protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements.

Principal Investigator:

Signed: _____ Date: _____

Name: Chang Chen

Title: MD., Ph.D.

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PROTOCOL SUMMARY

Title: Application of 3D printing technique in small pulmonary nodule localization: A Prospective, Randomized, Controlled, Non-inferiority Trial**.**

Objective: To evaluate the accuracy and safety of template-guided lung nodule localization compared to standard computed tomography (CT)-guided localization.

Participants: Surgical candidates with solitary pulmonary nodule <2 cm will be approached prior to scheduled lung resection. The necessity of preoperative nodule localization would also be evaluated by the patient's operating surgeon in charge. After acquiring patients' consent to participate into the study, enrolled patients will be randomized into the CT- or template-guided group using a previously generated random table. According to priori study, each group would have a sample size of 100 participants.

Number of site: This is a single-center trial and all participants would be recruited in Shanghai Pulmonary Hospital.

Description of Intervention: The three-dimensional printed, navigational template was created to guide percutaneous lung nodule localization. Its utility has been tested in previous feasibility trial.

Estimated Study Duration: From 01-10-2016 to 01-07-2019.

Estimated Time to Complete Enrollment: From 01-10-2016 to 01-06-2019.

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Schematic of Study Design

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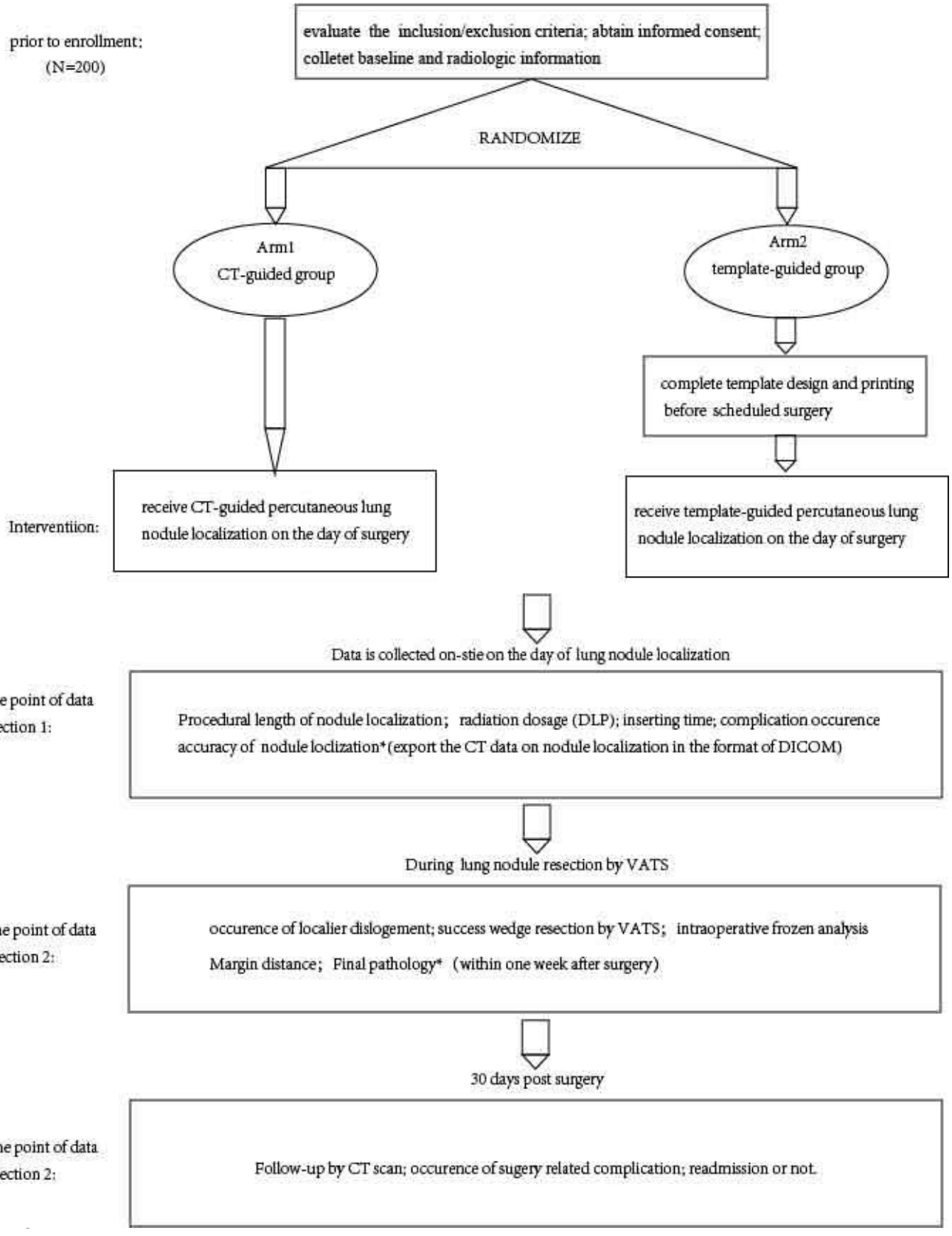

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LIST OF ABBREVIATIONS

3D	three-dimensional
CT	computed tomography
GGO	ground glass nodule
VATS	video assisted thoracoscopic surgery
DLP	dose-length product
ED	effective dosage

1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background information

With the widespread utilization of high resolution low-dosage CT scan in lung cancer screening, small lung nodules less than 1 cm in diameter are detected more often than ever. Biopsy resection by video-assisted thoracoscopic surgery(VATS) is an ideal option to diagnose and, at the same time, offer a curative intervention. In the dairy practice of thoracic surgery, small lung nodule resection by VATS has accounts for a large proportion.

Small-sized nodules, however, especially ground-glass opacity (GGO)-dominant nodules located deep in the lung parenchyma, are difficult to recognize during VATS. It was reported that failure of nodule localization is the most common reason leading to conversion to thoracotomy. In order to deal with this problem, there have developed many modalities to preoperatively localize the target lung nodule to facilitate nodule resection by VATS. Among those, percutaneous transthoracic lung nodule localization is the most frequently used approach because of its simplicity and independence of special equipment. Usually, the patients is taken into the CT room to receive lung nodule localization under CT guidance before the scheduled surgery. Despite its assistance in successful nodule resection by VATS, CT-guided percutaneous localization is sometimes arduous and requires many times of localizer redirection. Especially when the interventional radiologist is less experienced, it often takes many times of CT scans to accurately localize the target nodule.

With the purpose of facilitating nodule localization procedure and

reduce radiation exposure, a navigational template was created using three-dimensional (3D) printing technology and its utilization in clinical application has been preliminarily tested in previous study.

1.2 Rationale

The navigational template is created based on patient's CT images. Firstly, the CT data is downloaded from Picture Archiving and Communication Systems (PACS), then imported into the computer-aided design (CAD) software to reconstruct patient's thoracic digital model. According to this digital model, the navigational template was designed to mark the puncture site and angle of the localizer prior to nodule localization. In order to achieve accurate template placement on patient's thorax, several anatomical landmarks were marked on the template to check for template alignment.

With the assistance of navigational template, the practitioner does not need to manually calculate the inserting site and angle according to the two-dimensional image, but insert the localizer according to the guidance of template.

1.3 Potential Risks and Benefits

1.3.1 Potential Risks

The mechanism of template-guided lung nodule localization is the same as conventional CT-guided localization. Therefore, complications related to percutaneous lung nodule localization such as pain, pulmonary hemorrhage, pneumothorax, hemoptysis and so on, likely occur. Most of

these complication is non-significant and do not need special intervention.

For patient assigned to receive templated-guided nodule localization, the most worrying concern is the accuracy of lung nodule localization. Firstly, the previous feasibility trial has confirmed the precision of the navigational template, with 10.0 mm of the median localizer deviation and no occurrence of severe complications in template-guided localization. Secondly, for the sake of safety of participants in this trial , patients would receive CT scan to confirm the accuracy of the template-guided lung nodule localization after template placement but before localizer insertion.

Regarding to the concern of infection, the entire template was sterilized by UV irradiation for 30 minutes and the area adjacent to puncture point was sterilized using iodine. And the metal introducer sheath, through which the localizer was introduced, was sterilized using autoclave sterilizer. And infection of the puncture site was not found in our previous study. Additionally, as the template is made of nylon (PA3200), patients with a history of nylon allergy should not receive template-guided localization.

1.3.2 Potential Benefits

Based on our priori study, the application of 3D-printed template in lung nodule localization might facilitate the process of lung nodule localization. In template-guided lung nodule localization, radiologist do not need to measure the puncture site/angle/length from the two-dimensional CT images. Instead, the template pre-specified the insertion site and angle of the localizer. In this way, the practitioner may not need to take repeated attempts to redirecting the localizer, which leads to increased radiation exposure and high complication rate.

Therefore, patients receiving template-guided lung nodule localization would suffer less radiation exposure and lower complication rate. For the viewpoint of radiologist, the application of template significantly alleviates the challenge on practitioner and simplify the procedure of lung nodule localization. Lastly, the conventional CT-guided localization method requires the patients to stay still in one position during the whole procedure. It might be difficult for some patients, especially with obvious cough symptoms. However, in template-guided localization, the requirement about patient's position was not so strict. Patients might be more easily to cooperate in the template-guided lung nodule localization.

2 OBJECTIVES

2.1 Study Objectives

To evaluate the safety and accuracy of navigational template-guided method in percutaneous lung nodule localization.

2.2 Study Outcome

2.2.1 Primary outcome

The primary outcome of this study is the precision of the lung nodule localization, which was specified by the localizer deviation. As the center of the nodule is the designed target, localizer deviation is measured between the center of nodule and the localizer. Regarding to measurement of the localizer deviation, because the localizer and the target nodule might be not on the same section of the CT scan, it is impossible to accurately measure the deviation from two-dimensional images.

Therefor we reconstruct the CT images upon nodule localization into three-dimensional virtual model, and precisely measure the localizer deviation in three dimensions.

2.2.2 Secondary outcome

The secondary outcome includes procedural length, radiation exposure dosage and related complication rate.

In order to facilitate the process of data collection, the procedural length of nodule localization was inferred from CT scanning parameter. The time length of nodule localization is calculated from patients receiving the initial CT scan to patients receiving the last CT scan for complication evaluation. And, the radiation exposure dosage (dose-length-product) is directly collected from monitor screen after the last CT scanning. The complication related to percutaneous lung nodule localization mainly includes pneumothorax, pulmonary hemorrhage and hemoptysis during the time of waiting for surgery. The occurrence of pneumothorax and pulmonary hemorrhage is evaluated by CT scanning immediately after localizer release.

Additionally, localizer dislodgement rate and the margin distance reported on frozen analysis are also compared between patients undergoing CT-guided nodule localization and patients receiving template-guided nodule localization.

3 STUDY DESIGN

The study is designed to be a prospective, randomized, non-inferiority clinical trial comparing template-guided to CT-guided peripheral small lung nodule localization. The feasibility of template-guided lung nodule localization has already been confirmed in our previous study. The study is a phase II clinical trial and further examines the safety and efficacy of template-guided lung nodule localization.

3.1 Study population and groups

The randomized, controlled trial was approved by the institutional review board of Shanghai Pulmonary Hospital. Surgical candidates with solitary pulmonary nodule less than 2cm were prospectively recruited prior to scheduled lung resection. The necessity of preoperative nodule localization was also evaluated by patient's operating surgeon in charge. After acquiring patients' consent to participate into the study, patients were randomized into CT-guided group and template-guided group respectively.

3.2 Sample Size Calculation

The study was designed to confirm the non-inferiority of template-guided lung nodule localization compared to CT-guided lung nodule localization in terms of localization accuracy. And the accuracy of lung nodule localization was quantified by the localizer deviation between the

localization and the center of the target nodule.

The expected difference of localizer deviation between CT- and template-guided group was 3.5mm according to priori study. Deviation of 5mm is set as non-interiority margin. We needed to randomize 140 patients (70 each group) to give 90% power with one-sided alpha of 0.05. To allow for some dropouts, inclusion of 100 patients per group is planned.

3.3 Interim Analysis

An interim-analysis is performed on the primary and secondary outcomes when 40% of patients have been randomized. The interim-analysis is performed by an independent statistician, blinded for the treatment allocation. The data monitoring committee will have unblinded access to all data and will discuss the results of the interim-analysis in a joint meeting, and report to the ethics committee. Based on the results of interim-analysis, principal investigator decides whether the trial continues or not. The trial will be ended if the localizer deviation is significantly larger in template-guided lung nodule localization than CT-guided localization, and no benefit is obtained for patients undergoing template-guided lung nodule localization. Otherwise, the trial will be continued.

3.4 Time Schedule

The trail is planned to start in October 2016 and complete before July 2019, with about 10 patients enrolled per month. Patients will be followed up for one month after surgery to monitor postoperative complication.

3.5 Statistical Analysis

To decide whether the localization accuracy, radiation exposure and complication rate in the two groups are significantly different, three tests are used: 1) independent samples *t* tests for continuous variables that were normally distributed; 2) X^2 tests for categorical variables, and 3.)

Mann-Whitney U test for continuous variables that were not normally distributed.

Because of the possibility of patients withdraw, intention-to-treatment (ITT) analysis and efficacy analysis are both performed. ITT analysis is conducted for participants who received lung nodule localization and subsequent surgery. Efficacy analysis is only performed for patients who received lung nodule localization according to their assignment. All statistical analyses are two-tailed with a significance level of 0.05.

4 STYDT EBROLLMENT AND WITHDRAW

4.1 Inclusion Criteria

Patient scheduled lung nodule resection by VATS is assessed for eligibility. The inclusion criteria are as follows.

(1) The long-axis diameter of the target lung nodule is less than or equal to 20 mm;

(2) The inner edge of the target nodule is at least 2 cm away from major pulmonary arteries or veins to allow secure nodule excision;

(3) patient's surgeon in charge must confirm the necessity of preoperative lung nodule localization.

(4) Male or female ≥ 18years of age

4.2 Exclusion criteria

(1) There are more than two lung nodules which are needed to be localized for simultaneous resection.

(2) The target nodule is located in the scapula region; and percutaneous localizer is impeded by the scapula bone. Therefore, transthoracic percutaneous lung nodule localization is not suitable for this subset of patients.

4.3 Treatment Assignment Procedures

In order to randomly assign the participants to the two groups, a randomization list with 200 numbers was created using blocked randomization with a block size of 10. The 200 random numbers are each placed in sealed envelopes which are marked with sequential number at the cover.

Patients with scheduled lung resection are evaluated by research assistants. If the above criteria are met and patient's consent to participation has also been acquired, then the patient's information is sent to a person who is not involved with the trial by calling. Then, the accorded envelop is opened to assign the patient to template- or CT-guided localization group.

Because of the intrinsic property of the trial, no masking procedure is performed. After assignment, if the patient is allocated to template-guided lung nodule localization, research assistant needs to download the patients CT data from Picture Archiving and Communication Systems. The planned localization route is marked on CT images by patient's surgeon, then the CT data is emailed to designers for template design and printing. Because it takes about 6-8 hours for template production, all enrolled patents have to give consent to participate at least one day before the scheduled surgery.

4.6 Reasons for Withdrawal after Randomization

When patients are firstly approached by research assistants, they are informed that they have the right to withdraw their consent to participate at any stage of the trial without influence on their medical care. Therefore, patients with intended withdrawal after randomization is excluded from the study.

As the decision of lung nodule localization need to be made at more than one day before the scheduled surgery to allow for template production, there is the possibility of premature randomization, which is that the assigned patient might not suitable for lung resection after preoperative assessment. Patent whose scheduled lung resection is cancelled is withdrawn from the analysis.

5 STUDY INTERVENTION

All lung nodule localization procedures in both groups are performed under the surveillance of a Brilliance 40 CT scanner (Philips Medical Systems, Netherlands) by the same practitioner. And, the percutaneous transthoracic pulmonary nodule localization is conducted using the hookwire localization system (20 gauge, PAJUNK, Germany).

5.1 Control Group

Patients in the CT-guided group received conventional CT-guided percutaneous lung nodule localization using a hookwire system. After patients were positioned on the examining table of the CT scanner (patient's position was decided based on the location of the target nodule), the initial CT scan was conducted through the area of interest using a slice thickness of 3 mm. The localizer insertion site was determined by the CT gantry laser lights and a metal marker on the skin. The insertion length and angle were measured on CT images, and the localizer was then inserted without penetrating the pleura. Afterwards, repeated CT scans were taken to confirm or redirect the localizer in order to obtain adequate accuracy of nodule localization. Based on previous experience, deviations of $\leq$2 cm between the localizer and the center of the target nodule were considered accurate enough to allow for safe nodule localization. After confirmation of accurate localizer placement, the practitioner inserted the

localizer into the lung parenchyma and removed the cannula of hookwire.

5.2 Experiment Group

Patients in the template-guided group underwent template-guided percutaneous lung nodule localization using a hookwire. After template placement and prior to hookwire insertion, an initial CT scan is obtained to pre-evaluate the accuracy of nodule localization. If the deviation is less than 2 cm on the initial CT scan, the hookwire is inserted, and the localizer is deployed. However, if the deviation >2 cm based on the pre-evaluation on the initial CT scan, patients would receive conventional CT-guided localization.

After successful nodule localization, the CT scan is immediately obtained in order to evaluate the incidence and severity of the pneumothorax and hemorrhage in both groups. Afterwards, patients are wheeled back to the unit where they wait for the scheduled surgery. During the waiting period, patients are closely observed by nurses, and any occurrence of dyspnea and hemoptysis are detailly recorded.

6. Outcome Evaluation

The characteristics of nodule localization, including accuracy of nodule localization, procedural length, radiation exposure, and related complications are recorded on site by research assistant. Incidence of

localizer dislodgement and margin distance reported by frozen section analysis are collected during lung resection at the operative room.

6.1 Measurement of Localization Accuracy

The accuracy of nodule localization was defined by the deviation between the localizer and the center of the target nodule on CT images. Because the target nodule and localizer are in the three-dimensional space of a patient's thoracic cage, which may not be seen on the same cut of CT scan, it is difficult to precisely measure the deviation directly on the 2D images of CT scan. In order to accurately measure the deviation, computer-aided design (CAD) software is introduced to precisely measure the deviation.

Firstly, patient's thorax is reconstructed based on CT images upon nodule localization. Then the deviation is mathematically calculated using the CAD software.

6.2 Procedural Length

As the start/end point of lung nodule localization can be arbitrary and discrepancy between different researchers, procedural duration was derived from CT scan parameters, which is calculated as the time length between the initial and final scans.

6.3 Radiation exposure

The total amount of radiation exposure that patient receives during the lung nodule localization is quantified using dose-length product (DLP). And, the DLP value is directly displayed on the screen of the CT scanner after the scanning session. In order to estimate the relative amount of radiation dose, the effective dose (ED) is also calculated based on the DLP values (*Radiology;2008;248:995-1003*).

6.4 Complication Related to Nodule Localization

6.4.1 During lung nodule localization

All lung nodule localizations are conducted with presence of at least two researcher assistants to ensure the obedience of procedure protocol and collect complication information onsite. The occurrence of pneumothorax and pulmonary hemorrhage is immediately evaluated on the CT scan after the deployment of localizer. Other infrequent complications such as vasovagal response and hemoptysis are also recorded.

6.4.2 After localization prior to surgery

After lung nodule localization, patients are taken into the unit to wait for surgery. In this period of time, patients are monitored closely by nurses in case of the exacerbation of pneumothorax. And, occurrence of

hemoptysis and any other discomforts are detailed recorded.

6.4.3 During Surgery

Whether the target nodule is successfully resected by VATS with wedge resection is recorded by on-site researchers. During the VATS, the occurrence of localizer dislodgement is also recorded. After lung wedge resection, the margin distance reported by frozen section analysis is collected.

7. ETHICS AND PROTECTION OF HUMAN SUBJECTS

7.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the rules set by the Medical Equipment Specification for the Quality Control of Clinical Trial (*State Food and Drug Administration/National Health and Family Planning Commission/Number twenty-fifth*). All personnel involved in the conduct of this study have completed human subject protection training.

7.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB (*Shanghai pulmonary*

hospital affiliated to Tongji University) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

7.3 Informed Consent Process

Before the participants agree to participate into the trial, Informed consent is obtained in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects. A consent form describing in detail the study procedures and related risks would be given to the subject before participation. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study in detail to the participants and answer any questions that may arise. Subjects will sign the informed consent document before any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights

and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely compromised if they refuse to participate in this trial. The consent process will be documented in the clinical or research record.

8. DATA STORAGE POLICY

The principal investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators need to maintain adequate case histories of study subjects, including accurate case report forms (CRFs) and source documentation.

Data collection and accurate documentation are the responsibilities of the study staff under the supervision of the primary investigator. All source documents, laboratory results and CT images must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the primary investigator.

All the study documents and records should be stored for a minimum of 2 years after trial completion, which is required by the Medical Equipment Specification for the Quality Control of Clinical Trial

(*State Food and Drug Administration/National Health and Family Planning Commission/Number twenty-fifth*). No trial documents should be deliberately destroyed or damaged without consent of the IRB.