Minimally Invasive Transapical Septal Myectomy in the Beating Hearts for the Treatment of Hypertrophic Obstructive Cardiomyopathy: Safety and Efficacy Results of a Phase I First-in-man Clinical Trial

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1 Background

Hypertrophic cardiomyopathy (HCM) is the most common Autosome inherited heart disease that is characterized by obvious left ventricular hypertrophy, usually without enlargement (normal or narrowing) of the left ventricular cavity, and excludes other factors that can cause ventricular wall thickening. According to hemodynamics, HCM can be divided into hypertrophic obstructive cardiomyopathy and hypertrophic non-obstructive cardiomyopathy. Hypertrophic obstructive cardiomyopathy can be divided into left ventricular outflow tract obstruction (LVOTO), middle obstruction and apical obstruction according to the site of obstruction. According to epidemiological surveys, the crude prevalence of HCM in the overall population in China is 0.16%, the prevalence in men is 0.22% higher than that in women 0.10%, and the prevalence adjusted for age and sex is 0.08%, according to which it is estimated that there are more than 1 million HCM patients in China. The clinical manifestations of hypertrophic obstructive cardiomyopathy mainly include exertional dyspnea, chest pain, palpitations, and syncope. For patients with symptoms and the presence of LVOTO, the first-line treatment is medication. Patients who cannot effectively control symptoms despite sufficient medication can undergo invasive treatment, with surgical septectomy being the preferred treatment option for ventricular septal reduction. Foreign studies have shown that there is no statistically significant difference in 1-year, 5-year, and 10-year survival rates between patients with hypertrophic obstructive cardiomyopathy after surgery and the general population, and they are significantly better than patients who have not undergone surgery. Due to the limitations of conventional scalpel operation of traditional open-heart surgery to remove hypertrophic myocardial tissue, the difficulty of operation, angle and thickness of hypertrophic myocardial tissue resection are high, according to the "Guidelines for the Management of Hypertrophic Cardiomyopathy 2017", common complications in the early stage after surgical ventricular septectomy include ventricular septal perforation, aortic regurgitation and residual obstruction, so it is still necessary to explore safer and more effective treatment methods clinically.

In recent years, a number of minimally invasive treatments for HOCM have emerged, aiming to shorten the operation time, reduce trauma, reduce the incidence of surgery-related complications and their incidence, and improve the quality of life of patients. These include percutaneous ventricular septal alcohol ablation, percutaneous femoral ventricular septal radiofrequency ablation, percutaneous intramyocardial intraventricular septal radiofrequency ablation, etc. The main complications of percutaneous ventricular septal alcohol ablation

were perioperative death (perioperative mortality is 1.0%-1.4%), myocardial infarction at coronary artery injury and non-target ablation sites, intraoperative and postoperative ventricular arrhythmias. The main complication of percutaneous femoral ventricular septal radiofrequency ablation was complete atrioventricular block, and the proportion of complete atrioventricular block with percutaneous femoral septal radiofrequency ablation requiring dual-chamber pacemaker implantation was about 21.1%. Experience and long-term safety follow-up data on percutaneous intraventricular septal radiofrequency ablation are limited. Combining the limitations of traditional open-heart surgery and minimally invasive surgery, upgrading existing open-heart surgical instruments or upgrading existing surgical approaches is an effective way to explore safer and more effective treatment methods in the clinic.

2 Objectives

The primary purpose of this study is to evaluate the feasibility, the safety and the efficacy of the transapical beating-heart septal myectomy for the treatment of hypertrophic obstructive cardiomyopathy.

3 Beating-heart myectomy device

3.1 Beating-heart myectomy device

The BMD (Wei-Xin-Tan Cooperation, Wuhan, China) was constructed with a bullet-headed resection tube, a multi-functional handle, and a catheter connecting the chambers of the device. The resection tube was made of stainless steel and coated with polyurethane foam to eliminate acoustic artifacts under echocardiography. The resection tube was composed of an outer-layer sleeve tube, a tubular blade mounted inside the sleeve tube in a sliding fit, a paraxial puncture needle inside the tubular blade, and a multiporous tunnel outside the sleeve tube with a porous surface facing the tubular cavity. A resection window was formed on the sidewall in the head portion of the sleeve tube. The resection window was sealed by the tubular blade when the device was in the OFF state. Based on the length of the resection window and the diameter of the sleeve tube, a series of models of the BMD were fabricated with the following sizes (length–diameter in millimetres): 11–30, 11–40, 13–30, and 13–40.

Before entering the ventricular chamber, air in the device was evacuated by carefully flushing with normal saline through the catheter in the OFF state. Before resection, the puncture needle and the tubular blade were pulled back to switch the device to the ON state. The target myocardium and the resection window were brought together with the aid of negative pressure generated through the multiporous tunnel connecting the vacuum aspirator.

On aspiration, the puncture needle was pushed forward to puncture and capture the target myocardium. The tubular blade was then advanced to excise the captured myocardium and the device was returned to the OFF state. The resected myocardium, together with the BMD, were retrieved from the ventricular chamber, thereby completing one resection.

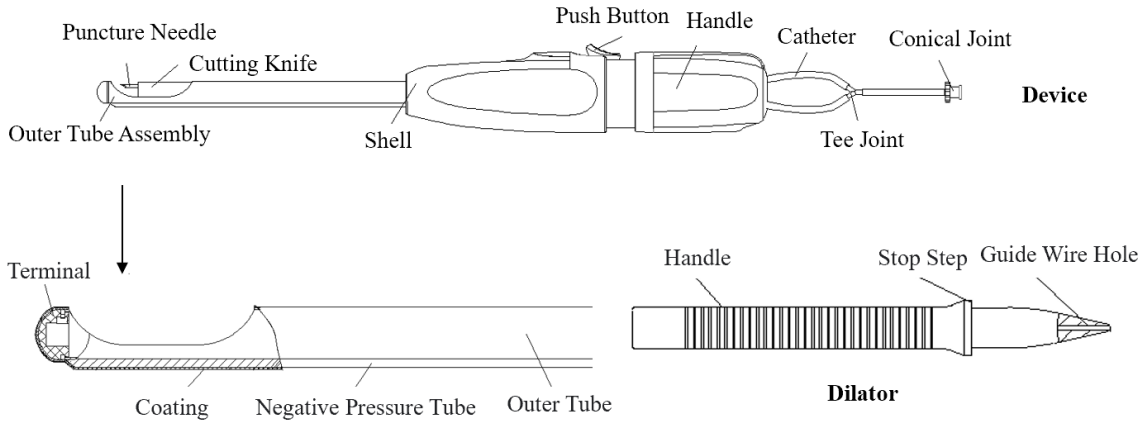

Figure 1. Structure diagram of the the beating-heart myectomy device

3.2 Surgical procedures

Surgery was performed under general anaesthesia in supine position. Mini-thoracotomy was mostly performed in the fifth and (less commonly) in the sixth intercostal space at the left midclavicular line, as determined by the transthoracic echocardiography-identified location of the LV apex (Central Illustration). Following incision and suspension of the pericardium, double-circumferential purse-string sutures with Teflon felt pledgets were placed in the avascular zone of the apex and secured with snares to provide haemostasis and LV entrance for the BMD (Central Illustration). Upon heparinisation, LV apical pressure, which represents the highest pressure generated by LVOT obstruction, was measured using a manometric catheter inserted through the purse-string. The systolic pressure gradient between the apical pressure and the peripheral arterial pressure, reflecting the LVOT gradient, was calculated. An isoproterenol provocation test (infused at 0.01-0.1 μg/kg/min) was performed if the resting LVOT gradient was less than 50 mmHg.

An apical puncture was produced inside the purse-string and was dilated using a dilator along a guidewire. After deairing, the BMD in the OFF state was introduced into the LVOT through the apical puncture under the navigation of transoesophageal echocardiography (Central Illustration). The location of the resection window was three-dimensionally identified by transoesophageal echocardiography. Specifically, the depth of the BMD tip was identified in the mid-esophageal long-axis view. The orientation of the resection window was

identified in the transgastric short-axis views at the basal and mid-ventricular levels. The first resection was performed in the basal anterior septum, which was located 5–10 mm beneath the aortic valve in the long-axis view, and to the midpoint of the septum in the short-axis view. Based on the first resection, the second resection was performed in the basal anterior septum parallel but slightly anterior to the first resection. The orientation of the second resection was identified on the short-axis view and was achieved by rotating the device 60–120°clockwise from the first resection. The morphology of the septal bulge, the LVOT gradient, the MR grade, and the remaining thickness of the target septum were evaluated after each resection. Subsequent resections were performed at the discretion of pre-procedural planning and real-time echocardiographic evaluations. In particular, excisions of the anterior and posterior septum were performed by rotating the BMD clockwise or anticlockwise from the location of the first resection in the short-axis view. Resections of the mid-ventricular septum were achieved by apically pulling the BMD from the basal segment in the mid-esophageal long-axis view. Additional resections were performed to tailor satisfactory improvements in the LVOT gradient, MR, and LV morphology. After completing the SM, the provocation test was repeated. Additional resections were performed if the provocation test was not satisfactory. The apical puncture was closed using the purse strings. A cell saver was used for blood reservation.

4 Endpoints

4.1 Primary endpoint

1. All-cause mortality at 3-month follow-up;
2. Procedural success: Resting left ventricle outflow tract gradients < 30 mmHg, provoked left ventricle outflow tract adients < 50 mmHg, and mitral regurgitation (MR) ≤ grade 1+ at 3-month follow-up.

4.2 Secondary endpoints

3. Device success

   Definition：uccessful accession, delivery, and retrieval of the resection device, successful resection of the septal myocardium, resting left ventricle outflow tract gradient less than 50 mmHg and mitral regurgitation (MR) ≤ grade 2+ during operation after resection, and free from conversion to midline thoracotomy during operation.
4. Septal thickness (at 7-day and 3-month follow-up)

   Basal and mid septal thickness as measured by echocardiography.

5. Left ventricle mass (at 3-month follow-up)
   Left ventricle mass index (the ratio of left ventricle mass to body weight) as measured by cardiac magnetic resonance.
6. Left ventricle volume (at 3-month follow-up)
   Left ventricle end-diastolic volume as measured by echocardiography.
7. Cardiac diastolic function (at 7-day and 3-month follow-up)
   The ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e') as measured by echocardiography.
8. Left atria volume (at 3-month follow-up)
   The left atria volume as measured by echocardiography.
9. New York Heart Association class (NYHA) (at 7-day and 3-month follow-up)
   New York Heart Association class, including grade I, grade II, grade III, grade IV. A higher grade means worse heart function.
10. 6-minute walking test (at 3-month follow-up)
    6-minute walking test. A longer distance means better heart function.
11. Heart function-associated quality of life (at 3-month follow-up)
    Score of the Kansas City Cardiomyopathy Questionnaire. A higher score means better heart function.
12. Left ventricular outflow tract gradient (at 7-day and 3-month follow-up)
    Left ventricular outflow tract gradient as measured by echocardiography.
13. Evaluation of the mitral valve (at 7-day and 3-month follow-up)
    Grade of mitral regurgitation and systolic anterior motion as measured by echocardiography.
14. Left ventricular outflow tract diameter (at 7-day and 3-month follow-up)
    Left ventricular outflow tract diameter as measured by echocardiography.

4.3 Secondary safety endpoints

4.3.1 Adverse events

1. All-cause mortality and sudden cardiac death within 30 days after operation;

2. Adverse event rate during operation and within 30 days after operation (complete heart block requiring permanent pacemaker implantation, sternotomy conversion, iatrogenic ventricular septal perforation, iatrogenic valvular injury, and imaging examination-validated cerebral complications, etc.) and the total number of incidents that occurred;

3. Incidence rate (%) and number of (serious) adverse events related to surgery and

equipment during operation and within 30 days after operation.

4.3.2 Abnormal vital signs and laboratory tests

1. General indicators: body temperature, heart rate, respiration, blood pressure;

2. Abnormal results of laboratory tests: blood routine, urine routine, liver and kidney function (ALT, AST, Cr, BUN);

5 Statistical Analysis

5.1 Analysis sets

(1) Full analysis set (FAS)

According to the intention-to-treat (ITT) principle, all cases that have been treated and have at least one follow-up record constitute the FAS of this study.

(2) Per-protocol set (PPS)

The criteria for the PPS set and its population will be finalized during data blind verification, including at least the following criteria: compliance with the inclusion criteria specified in the trial protocol; completion of the treatment protocol without serious protocol deviation, and evaluable efficacy indicators.

(3) Safety set (SS)

All enrolled patients who have undergone treatment and have recorded safety indicators constitute the safety population of this study.

The curative effect evaluation of this study was analyzed by FAS and PPS. SS is the main population for the safety evaluation of this study.

5.2 Analysis methods

(1) General principles: A two-sided p-value of less than 0.05 was considered statistically significant.

(2) Statistical description: Normal distribution of continuous variables was assessed by Kolmogorov–Smirnov test. Continuous normal distributed variables were presented as means (standard deviation). Continuous non-normal distributed data were expressed as medians (interquartile ranges, IQR). Categorical variables were presented as counts and percentages.

(3) Statistical analysis method: Continuous normal distributed variables of repeated measurements were compared using matched *t*-test for two groups and the repeated measures ANOVA for multiple groups. Continuous non-normal distributed variables were compared using Wilcoxon signed ranks test for two group and Friedman test for multiple groups. Repeated measurements of one-way ordered ranking data were compared using Friedman

test.

(4) Dropout analysis: Count the dropout/rejection rate and the reasons.

(5) Effectiveness analysis: Count the number and percentage of deaths at 3-month follow-up. Count the number and percentage of procedural success cases.

(6) Safety analysis: Calculate the incidence of adverse events, and list and describe the adverse events that occurred in this trial and their associations with the devices.

Statistical analyses are done using the SPSS software (version 23.0).

6 Overall design

6.1 Trial design

This is a prospective, single-arm, single-center, first-in-man study.

6.1.1 Sample size determination

This study plans to recruit 50 subjects.

6.1.2 Primary Purpose

The primary purpose of this study is to evaluate the feasibility, the safety and the efficacy of the transapical beating-heart septal myectomy for the treatment of hypertrophic obstructive cardiomyopathy.

6.1.3 Follow-up visit point

The total follow-up period of the trial is 3 months, with 5 visits conducted during the screening/baseline period (-7~0 days), surgery day (day 0), visit 3 (postoperative day 1), visit 4 (postoperative day 7 ±2 days), and visit 5 (postoperative month 3 ± 7 days). The efficacy evaluation at the main time point is on the day of surgery (day 0).

6.1.4 Medical devices

Devices Name: Transapical beating-heart septal myectomy

Product Model：TASM-1130、TASM-1140、TASM-1330、TASM-1340

Model	Outer pipe diameter D（mm）	Cut slot length L0（mm）	Effective length of outer tube L(mm)	Expander head width D2(mm)
TASM-1130	11	30	170	11.5±1
TASM-1140	11	40	170	11.5±1
TASM-1330	13	30	170	13.5±1

TASM-1340	13	40	170	13.5±1

6.1.5 Subject selection

6.1.5.1 Study population

Patients with hypertrophic obstructive cardiomyopathy accompanied by symptoms of left ventricular outflow tract stenosis.

6.1.5.2 Inclusion Criteria

1) Patients whose resting or provoked left ventricular outflow tract gradient>50 mmHg, and maximal ventricular septal wall thickness ≥ 15 mm.

2) Patients with heart function of New York Heart Association ≥ class II.

3) Patients with drug-refractory symptoms or intolerable to pharmaceutical therapies.

4) Patients who was informed the nature of the clinical trial, consented to participate in all of the activities of the clinical trial, and signed the informed consent form.

6.1.5.3 Exclusion Criteria

1) Patients who were pregnant.

2) Patients who had concomitant diseases such as intrinsic valvular disease or coronary artery disease that needed open-heart surgery.

3) Patients who had severe heart failure with left ventricle ejection fraction < 40%.

4) Patients whose estimated life expectancy < 12 m.

5) Patient who were non-compliant.

6) Patients under circumstances which were considered not suitable or prohibitive for participating the clinical trial at the discretion of the attending medical team and the researchers.

6.1.5.4 Delete Criteria

Principal Investigator, the Sponsor and the Statistical Organ determine whether a subject is excluded before statistical analysis of data. In case of any of the following circumstances, Principal Investigator shall determine whether to exclude the subject according to the completion degree of the trial and withdrawal reason, and make appropriate explanations.

1) The subject shall be excluded in case of violating inclusion/exclusion criteria;

2) During the trial, the investigator stops the subject from continuing to participate in the trial, thinking the subject is subject to other factors that preclude him/her from continuing the trial;

3) The subject changes the treatment protocol during the trial;

4) During the trial, the subject doesn't comply with trial schedule and has poor compliance, such as never use of the investigational product, or failure to collect samples for efficacy and safety evaluation according to the trial protocol, or unavailability of any data.

6.1.5.5 Criteria and procedures of withdrawal/termination of the trial

Criteria of withdrawal/termination of the trial:

It refers to that the subject discontinues the trial instead of completing the trial as required by the protocol. The objective of discontinuation is to safeguard the subject's benefit, ensure trial quality and avoid unnecessary economic loss. The investigator determines that the subject can not continue the clinical trial, in case of the following circumstances:

1) The subject is lost to follow-up or requests for withdrawal;

2) In case of clinical adverse events (AEs), abnormal laboratory test or comorbidity, the investigator doesn't think that continuation meets the subject's best benefit;

3) Other circumstances that the investigator thinks withdrawal is necessary, such as the subjects losses ability to express willing due to imprisonment or quarantine;

4) Circumstances that the Sponsor thinks discontinuation is necessary, such as not meeting inclusion criteria, failure to implant devices as required or receiving other interventions that influence the subject's safety or evaluation of the trial results;

5) Circumstances that discontinuation is necessary due to other reasons; and

6) The subject dies.

The subject has the right to withdraw from the trial at any time without any reason. If the subject decides to withdraw from the trial, the investigator shall try to find out the reason for withdrawal and record the reason as original text data.

The investigator has the right to discontinue the subject's participation in the trial when the following circumstances occur: The investigator must carefully evaluate the subject who discontinues the trial, take positive treatment measures, and record in detail in original records. If the subject withdraws from the trial due to AEs, abnormal laboratory test or test failure, it must also be evaluated and treated accordingly, and be recorded in detail in original records. The investigator can also determine whether the subject should continue the clinical trial based on medical judgment at any time during the trial.

Criteria of termination of the trial：

Termination of the trial means that the trial is stopped before completing evaluation of all subjects as planned. After the trial is terminated, new subjects will not be included. The subjects who have been included but not yet dropped out will be checked and interviewed

according to the results of the discussion between the Sponsor and the investigator.

1) If no clinical value of the product is found during the trial, the trial shall be terminated;

2) If any major error in the clinical trial protocol is found during the trial and it's difficult to evaluate product effect, the trial shall be terminated;

3) If severe deviation occurs during the trial, and it's difficult to evaluate product effect if the trial continues, the trial shall be terminated;

4) The Sponsor requests termination (due to the reason of funding or management);

5) NMPA orders to terminate the trial due to some reasons;

6) Ethics Committee terminates the trial to safeguard the rights and interests of the subjects.

If any subject terminates the trial prematurely, the investigator should try to find out the reasons for withdrawal, such as AEs, ineffective correction measures, withdrawal based on the investigator's decision or other reasons. The reasons of withdrawal shall be recorded in CRF.

It is necessary to complete efficacy and safety evaluation when withdrawal or termination of the trial occurs as specified in the protocol, complete safety follow-up, and record AEs and outcomes completely. The investigator can advise or provide new or alternative therapies to the subject according to actual situation of the subject.

If the subject refuses to go to the study site for further visit, study-related information shall be collected continuously, unless the subject withdraws the consent of disclosing further information or being contacted. In this case, no more evaluation shall be conducted and no more data shall be collected.

Premature termination or suspension：

The present study can be terminated or suspended prematurely. This may be due to the decision of regulatory authority, change of opinions of Ethics Committee, efficacy or safety of the investigational drug, or decision of the Sponsor. In addition, the Sponsor who decides to suspend/terminate the study will send a written notice and reasons for termination or suspension of the study to the investigator, the Sponsor and regulatory authority. The investigator should notify Ethics Committee and the Sponsor, and clarify relevant reasons immediately.

Reasons for premature termination or suspension of the study may include:

- Definite unexpected, major or unacceptable risks facing the subject.

- Existing efficacy results support premature termination of the study.
- Low compliance as required by the protocol.

Once the problems mentioned above are resolved, the study can be continued upon approval by the Sponsor, Ethics Committee or regulatory authority. .

6.1.5.6 Expected duration of the clinical trial and rationale

Personnel training will begin after the Sponsor and medical institute of the clinical trial sign the clinical trial protocol through amicable negotiations. Case observation record will be printed according to defined evaluation criteria of the investigational product. The Sponsor will provide sufficient investigational products, and take into account relevant factors such as the patient referral rate and the number of patients who agree to participate in the trial. As planned, the clinical trial will start upon approval by the Ethics Committee and the signing of clinical trial agreement Fifteen patients are expected to be enrolled from January 2022 to December 2023. Summary of clinical study will be completed in February 2024. Duration of the trial will be modified according to actual progress of the trial. If all cases are not completed, the trial will be postponed until all cases have been completed.

6.1.5.7 Expected duration of participation of each subject

The duration of participation of each subject is defined as the period of time from the subject's signing the informed consent to the end of final follow-up. In this trial, the expected duration of participation of each subject is 3.3 months, including 1 week of screening, 1 day of surgery and 3 months of following up.

6.1.6 Evaluation Index

6.1.6.1 Explanation of Outcome Measures

Primary Outcome Measure:

1) All-cause mortality

Death from any cause during the observation period.

[Time Frame: 3 months]

2) Procedural success

Resting left ventricle outflow tract gradients < 30 mmHg, provoked left ventricle outflow tract gradients < 50 mmHg, and

mitral regurgitation (MR) ≤ grade 1+.

[Time Frame: 3 months]

Secondary Outcome Measure:

3) Device success

Successful accession, delivery, and retrieval of the resection device, successful resection of the septal myocardium, resting left ventricle outflow tract gradient less than 50 mmHg and mitral regurgitation (MR) ≤ grade 2+ during operation after resection, and free from conversion to midline thoracotomy during operation.

[Time Frame: 1 day]

4) Septal thickness

Basal and mid septal thickness as measured by echocardiography.

[Time Frame: 7 days and 3 months]

5) Left ventricle mass

Left ventricle mass index (the ratio of left ventricle mass to body weight) as measured by cardiac magnetic resonance.

[Time Frame: 3 months]

6) Left ventricle volume

Left ventricle end-diastolic volume as measured by echocardiography.

[Time Frame: 7 days and 3 months]

7) Cardiac diastolic function

The ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e') as measured by echocardiography.

[Time Frame: 7 days and 3 months]

8) Left atria volume

The left atria volume as measured by echocardiography.

[Time Frame: 7 days and 3 months]

9) Major adverse cardiovascular and cerebral events

In-hospital mortality, atrioventricular block that need permanent pacemaker implantation, sternotomy conversion, iatrogenic ventricular septal perforation, iatrogenic valvular injury, imaging examination-validated cerebral complications.

[Time Frame: 3 months]

10) New York Heart Association class

New York Heart Association class, including grade I, grade II, grade III, grade IV. A higher grade means worse heart function.

[Time Frame: 7 days and 3 months]

11) 6-minute walking test

6-minute walking test. A longer distance means better heart function.

[Time Frame: 3 months]

12) Heart function-associated quality of life

Score of the Kansas City Cardiomyopathy Questionnaire. A higher score means better heart function.

[Time Frame: 7 days and 3 months]

13) Left ventricular outflow tract gradient

Left ventricular outflow tract gradient as measured by echocardiography.

[Time Frame: 7 days and 3 months]

14) Evaluation of the mitral valve

Grade of mitral regurgitation and systolic anterior motion as measured by echocardiography.

[Time Frame: 7 days and 3 months]

15) Left ventricular outflow tract diameter

Left ventricular outflow tract diameter as measured by echocardiography.

[Time Frame: 7 days and 3 months]

6.1.6.2 Evaluation of Device Performance

- The investigator evaluates the operation performance of study device intraoperatively, according to the following evaluation criteria:

  - **Excellent**: The device is easy to operate without error touch. It can quickly and precisely puncture and fix the tissue to be resected and remove it. Negative pressure aspiration is successful. There is no tissue detachment or debris generation during removal. The cutting edge of the removed tissue is regular and free of burrs. The device does not interfere with ultrasound. The intraoperative positioning is precise.

  - **Good**: The device is easy to operate without error touch. It can precisely puncture and fix the tissue to be resected. Negative pressure aspiration is successful. There is no tissue detachment or debris during removal. The cutting edge of the removed tissue is regular and free of burrs. The device does not interfere with ultrasound. Intraoperative positioning is precise.

  - **Medium**: The device enables smooth operation with ≤3 intraoperative error touches. It can puncture and fix the tissue to be resected. Negative pressure aspiration is successful. There is basically no tissue detachment or debris generation during removal. The cutting edge of the removed tissue is relatively regular without obvious burr. The device interferes with ultrasound, but there is no impediment in intraoperative positioning.

  - **Poor**: Use of the device in left ventricle is difficult with multiple (>3) error

touches. Puncturing and fixation of the tissue to be resected are difficult. Negative pressure aspiration is not satisfactory. There is tissue detachment or debris generation during removal. The cutting edge of the removed tissue is not regular with obvious burr. The device interferes with ultrasound significantly. Intraoperative positioning is difficult.

6.1.6.3 Description of Safety Parameters

1) All-cause mortality rate and sudden cardiac death rate within 30 days after surgery;

2) Incidence of severe AEs (severe pericardial effusion, arrhythmia, aortic valve injury, mitral valve injury, ventricular septal defect, ischemic cerebral infarction, apical tear, hemorrhagic shock) within 30 days after surgery and number of events;

3) Incidence (%) of surgery and device-related (serious) AEs within 30 days after surgery, and number of events.

6.1.6.4 Method and time for evaluation, recording and analysis of parameters

- **AEs: all-cause mortality rate and sudden cardiac death rate within 30 days after surgery**

AEs refer to adverse medical events during the clinical trial, which are related or unrelated to the medical device used. All-cause mortality and sudden cardiac death within 30 days after surgery are key events of monitoring. The incidence of AEs is calculated with the sum of AEs in all subjects as the numerator and number of included cases with all evaluable AEs as the denominator.

- **Incidence of severe adverse events within 30 days after surgery**

Serious AEs (SAEs) refer to the events that occur during the clinical trial and lead to death or severe worsening of health, including fatal diseases or injury, permanent defect of physical structure or functions, hospitalization or extension of hospitalization, medical or surgical intervention to avoid permanent defect of physical structure or functions; or the events leading to fetal distress, fetal death, congenital abnormality, congenital defect, etc.

SAEs that may occur during this study include severe pericardial effusion, arrhythmia, aortic valve injury, mitral valve injury, ventricular septal defect, ischemic cerebral infarction, apical tear, hemorrhagic shock, etc. The incidence of SAEs is calculated with the sum of SAEs in all subjects as the numerator and the number of included cases with all evaluable SAEs as the denominator.

❖ Time points of visits: Screening/baseline (Day -7 to Day 0), the day of surgery (Day 0), Visit 3 (1 day after surgery), Visit 4 (1 week ± 2 days after surgery), Visit 5 (1 month ± 3 days after surgery).

- **Incidence (%) of surgery and device-related (serious) AEs within 30 days after surgery and number of events**

Device defects refer to unreasonable risks that may endanger human health and life safety in normal use of medical devices in clinical trials, such as label errors, quality problems, failures and other events. The incidence (%) of surgery and device-related (serious) AEs refers to the incidence of surgery and device-related adverse medical events or AEs. The incidence of device-related (serious) AEs is calculated with the sum of surgery and device-related (serious) AEs as the numerator and the number of included cases with all evaluable AEs as the denominator.

6.2 Trial Process

6.2.1 Trial Process

Visit 1: Screening/Baseline Period (-7-0 days)

1) Sign an informed consent form;

2) Record past or current medical history, accompanied by disease and treatment history, family history, surgical history, trauma history, allergic history

3) Verify inclusion/exclusion criteria;

4) Demographic data: including gender, age (date of birth), ethnicity, and weight;

5) Vital signs include body temperature, respiration, heart rate, and blood pressure;

6) Physical examination: including general conditions, skin and mucous membranes, lymph nodes, head, neck, chest, abdomen, spine and limbs, nervous system, and other routine examinations;

7) Blood routine: Red blood cell, white blood cell, platelet count, hemoglobin, percentage of neutrophils, percentage of lymphocytes;

8) Urinary routine: urine sugar, urine pH, bilirubin, urine protein, urine ketone body, urine specific gravity, red blood cell count, white blood cell count;

9) Blood biochemistry: liver function, kidney function, electrolytes, including enzymes such as glutathione aminotransferase, alanine aminotransferase, total protein, albumin, globulin, total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase γ-Glutamyltranspeptidase, total cholesterol, lactate dehydrogenase, urea, creatinine, uric acid, hydrocarbon, eGFR, potassium, sodium, chloride, calcium, corrected calcium;

10) Coagulation function: prothrombin time, prothrombin activity, international standardized ratio, fibrinogen, activated partial thromboplastin time, thrombin time;

11) Echocardiography: Left ventricular outflow tract pressure difference (LVOTG), left

ventricular outflow tract diameter, end diastolic interventricular septal thickness, end diastolic left ventricular diameter, end systolic left ventricular diameter, end diastolic left ventricular volume, end systolic left ventricular volume, left ventricular ejection fraction, diastolic mitral valve E-peak and A-peak velocities;

12) Cardiac MRI or chest enhanced CT

13) Myocardial enzymology: High sensitivity cardiac troponin I, myoglobin, creatine kinase MB type isoenzymes;

14) B-type natriuretic peptide;

15) Electrocardiogram;

16) NYHA assessment;

17) 6-minute walking test;

18) Quality of life score;

19) Evaluation of combined medication use;

20) Adverse event evaluation: Record the adverse events/serious adverse events that occurred/existed during the screening period of the subjects;

21) Make an appointment for the next visit.

Note: The laboratory examination results and imaging results (echocardiography) within 7 days and 30 days prior to signing the informed consent are both valid

Visit 2: On the day of surgery (Day 0)

1) Verify inclusion/exclusion criteria;

2) Surgical records;

3) Echocardiography: Left ventricular outflow tract pressure difference (LVOTG), left ventricular outflow tract diameter, end diastolic interventricular septal thickness, end diastolic left ventricular diameter, end systolic left ventricular diameter, end diastolic left ventricular volume, end systolic left ventricular volume, left ventricular ejection fraction, diastolic mitral valve E-peak and A-peak velocities;

4) Electrocardiogram;

5) Immediate success evaluation after surgery;

6) Product device performance evaluation;

7) Record the situation of combined medication use;

8) Record the occurrence of adverse events;

10) Make an appointment for the next visit.

Visit 3: 1 day after surgery

1) Vital signs: body temperature, respiration, heart rate, blood pressure

2) Electrocardiogram;

3) Record the situation of combined medication use;

4) Record the occurrence of adverse events;

6) Make an appointment for the next visit.

Visit 4: 1 week ±1 day after surgery

1) Vital signs: body temperature, respiration, heart rate, blood pressure;

2) Blood routine: Red blood cell, white blood cell, platelet count, hemoglobin, percentage of neutrophils, percentage of lymphocytes;

3) Urinary routine: urine sugar, urine pH, bilirubin, urine protein, urine ketone body, urine specific gravity, red blood cell count, white blood cell count;

4) Blood biochemistry: liver function, kidney function, electrolytes, including enzymes such as glutathione aminotransferase, alanine aminotransferase, total protein, albumin, globulin, total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase γ-Glutamyltranspeptidase, total cholesterol, lactate dehydrogenase, urea, creatinine, uric acid, hydrocarbon, eGFR, potassium, sodium, chloride, calcium, corrected calcium;

5) Echocardiography: Left ventricular outflow tract pressure difference (LVOTG), left ventricular outflow tract diameter, end diastolic interventricular septal thickness, end diastolic left ventricular diameter, end systolic left ventricular diameter, end diastolic left ventricular volume, end systolic left ventricular volume, left ventricular ejection fraction, diastolic mitral valve E-peak and A-peak velocities;

6) Cardiac MRI or chest enhanced CT;

7) B-type natriuretic peptide;

8) Electrocardiogram;

9) NYHA assessment;

10) Quality of life score;

11) Record the situation of combined medication use;

12) Record the occurrence of adverse events;

14) Make an appointment for the next visit.

Visit 5: 3 months ±7 days after surgery

1) Vital signs: body temperature, respiration, heart rate, blood pressure;

2) Blood routine: red blood cells, white blood cells, platelet count, hemoglobin, percentage of neutrophils, percentage of lymphocytes

3) Blood biochemistry: liver function, kidney function, electrolytes, including enzymes such as glutathione aminotransferase, alanine aminotransferase, total protein, albumin,

globulin, total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase γ-Glutamyltranspeptidase, total cholesterol, lactate dehydrogenase, urea, creatinine, uric acid, hydrocarbon, eGFR, potassium, sodium, chloride, calcium, corrected calcium;

4) Echocardiography: Left ventricular outflow tract pressure difference (LVOTG), left ventricular outflow tract diameter, end diastolic interventricular septal thickness, end diastolic left ventricular diameter, end systolic left ventricular diameter, end diastolic left ventricular volume, end systolic left ventricular volume, left ventricular ejection fraction, diastolic mitral valve E-peak and A-peak velocities;

5) Cardiac MRI or chest enhanced CT;

6) Myocardial enzymology: High sensitivity cardiac troponin I, myoglobin, creatine kinase MB type isoenzymes;

7) B-type natriuretic peptide;

8) Electrocardiogram;

9) NYHA assessment;

10) Quality of life score;

11) 6-minute walking test;

12) Record the situation of combined medication use;

13) Record the occurrence of adverse events.

6.2.2 Standard use of device

6.2.2.1 Auxiliary devices

1) 18G vascular puncture needle, 0.035 inch short wire

2) Echocardiogram

3) Negative pressure flushing and aspiration system

All these auxiliary devices are (possibly) medical devices used during the surgery. Validation of compatibility with the product dilator is necessary before use of puncture and wire. In addition, this device is a myocardial resection device, and compatibility with other devices shall be validated before use. Surgical operation is performed as per the instructions.

6.2.2.2 Operation methods

- **Preparation of patients**

1) The patient is in supine position. After disinfection of surgical field, make a small incision of 3-5 cm in left 5th rib under general anaesthesia;

2) Open the pericardium and expose left ventricular apex. Place two purse-string sutures in advance 2 cm lateral end of left anterior descending branch.

- **Preparation of device**

1) Read and understand the instructions.

2) Ensure intact packing and sterilization within expiry.

Warning: Do not use if the packing is broken or opened.

3) Take out the device from the sterile package, perform sterile operation, check the integrity of the product, and confirm that the resection slot is fully closed. If it is not completely closed, push the rear part of the handle to completely close the resection slot.

Note: Do not use the device if it is broken, puncture needle is exposed or the safety device is in unlocked position. Failure of keeping the device and auxiliary device sterile may lead to infection.

- **Operation of device**

1) Use the 18G vascular puncture needle to perform apical puncture in the purse-string suture. Insert a 0.035-inch short wire into the heart for guidance. After removal of the puncture needle, hold the handle of the dilator, and insert the dilator into the apex pole along the wire for dilation. When the stopper of the dilator contacts the heart, dilation is completed;

2) Fill 50 ml normal saline to expel internal air through a flexible pipe;

3) Remove the dilator and tighten up the purse-string suture to stop bleeding. Insert the minimally-invasive myocardial resection system through the apical pole slowly into left ventricular outflow tract along the interventricular septum under ultrasound monitoring;

4) Under real-time ultrasound monitoring, align the resection slot with the site to be resected, reverse the handle, push the button, open the resection slot, and ensure that there is no other cardiac structure in the resection slot except hypertrophic myocardial tissue;

5) Apply a certain pressure to the resection slot, turn on the negative pressure system to a negative pressure -0.07 Mpa, and place the tissue to be resected completely into the resection slot. At this time, press the button downward and push the button forward to the front end to fix the tissue to be resected. Note that during the pushing process, keep the device still and close to the resected site;

6) After the puncture needle is in place, the handle is rotated left and right to resect under real-time ultrasound monitoring. When the handle is rotated and pushed to the front end, the resction is completed. Take out the minimally-invasive cardiac resection system under ultrasound monitoring, tighten the apical purse-string suture to stop bleeding, turn off the negative pressure system, step back the handle and push button in turn, open the resection slot and take out the rescted tissue.

7) Left ventricular outflow tract gradient (LVOTG) is measured by ultrasound. If the hypertrophic ventricular septal myocardial tissue needs to be resected again, the resection slot should be thoroughly cleaned to ensure that there are no residual myocardium, tissue fragments, blood clots in the resection slot. Restore the device to the original state, and then repeat above steps 2, 3, 4, 5, and 6 for resection.

6.2.3 Monitoring Plan

According to the complexity of the trial and number of sites, the Sponsor shall assign qualified monitors and formulate corresponding monitoring plans to ensure that the rights and interests of subjects in the clinical trial are protected, data of trial records and reports are accurate and complete, and the trial complies with approved protocol and relevant regulations.

Pre-trial monitoring items include devices, study documents, study staff and study training. Items of monitoring during trial include screening of subjects, informed consent, routine visits, documents to be submitted to the Ethics Committee during the trial, and adverse events. Items of monitoring at (Premature end) the end of trial include recovery of investigational products, recovery of CRF and data query, confirmation of the integrity of study documents, notification of Ethics Committee, review of AE and SAE, closure of sites, statistical analysis reports of clinical trials, and clinical trial reports.

The monitor shall have relevant professional background in clinical medicine, pharmacy, biomedical engineering and statistics, be familiar with management specifications and relevant regulations for clinical trials of medical devices after necessary training, as well as non-clinical information of study medical device, clinical information of similar products, and also clinical trial protocol and relevant documents.

The monitoring frequency in the approved Monitoring Plan shall prevail.

The monitor shall comply with Good Clinical Practice (GCP) principles, and ensure that the clinical trial is strictly conducted as per the protocol through effective supervision. Trial data are authentic, integral and accurate. Specific responsibilities include:

(1) Confirm that the clinical study site has appropriate conditions before the trial, including staffing and training, complete laboratory equipment, good working conditions, sufficient number of subjects, and participants familiar with the trial requirements;

(2) Monitor whether the clinical study site and investigator comply with approved clinical trial protocol, Good Clinical Practice of medical device or relevant regulations before, during and after the trial;

(3) Confirm that each subject signs the informed consent before participating in the trial; understand the enrollment rate and progress of the trial; record the trial and test that the investigator doesn't conduct and correction of errors and omissions clearly and actually; and confirm that subjects whose visits aren't completed to re-sign the revised informed consent;

(4) Confirm that all CRFs are filled correctly and consistent with original data. All errors or omissions have been corrected or noted, signed and dated by the researcher. The type of disease, total number of cases, age and effectiveness in each trial shall be confirmed and recorded;

(5) Confirm that withdrawal or non-compliance with the informed consent is recorded, and discuss the case with the investigator;

(6) Confirm that all adverse events and device defects should be recorded, and SAEs and major device defects that may lead to SAEs should be reported and recorded within specified time;

(7) Monitor the supply, use and maintenance of the study medical devices and treatment process of medical devices after trial;

(8) Ensure that the equipment related to clinical trial evaluation is regularly maintained, calibrated and recorded;

(9) Ensure that the investigator receives the latest copies of all documents related to the clinical trial;

(10) A written report shall be submitted to the Sponsor and clinical study site after each monitoring. The report shall indicate the date and time of monitoring, name of the monitor, location of monitoring, name of the investigator, monitoring content, completion of the trial, monitoring findings, facts, deviations, conclusions and correction of errors and omissions.

7 Risk analysis and countermeasures

7.1 Analysis of each subject before enrollment

Before enrollment of each subject, it is necessary to perform a thorough risk analysis, describe in detail the type of risk, estimate the severity, and demonstrate the possibility to

minimize the risk and the rationality between risk and expected benefit. Risk analysis scope covers expected benefits and potential clinical effects of failure identified in equipment evaluation strategy, as well as the risks or inherent processes that may be related to potential disease, are not related to the equipment, and benefit from the unique equipment design.

7.2 Common risk types and manifestions of study devices

7.2.1 Types of device defect

Types of device defects include but are not limited to defects of device design, defects of manufacturing and packaging process, operation defects, and clinical application accidents caused by patients' special anatomical characteristics.

7.2.2 Possible defects of study device

Include:

- Cutting knife fails to work normally, resulting in device failure and surgery failure
- The puncture force of the puncture component is too small, resulting in failure of the device to puncture and fix the tissue and also difficulty of subsequent surgery
- Air-tight seal is not up to standard, the negative pressure aspiration fails, and fixation of tissue and subsequent surgery are difficult
- The cutting knife does not move smoothly, the cutting edge is not regular with many burrs, and the detached tissue forms plug during cutting process
- Surface coating interferes with ultrasound imaging and forms ultrasound artifacts, resulting in difficulty of ultrasound-guided surgery in Surgery II
- The product material is corroded in blood environment, this causes the release of harmful substances and detachment of particles, and substances produced by reaction between the product and tissue fluid cause adverse reactions of patients
- The handle control is slow or the button fails, resulting in device failure and surgery failure

7.3 Methods to minimize risk

Standard methods and additional mitigation strategies may be adopted to protect individual subjects and future participants. Examples of standard and additional risk mitigation strategies include:

7.3.1 Study site that provides appropriate therapy

A study site that provides appropriate alternative therapy when necessary and manages

AEs with sufficient expertise and resources.

7.3.2 Fully trained and qualified investigators

Confirm that fully trained and qualified investigators can conduct early feasibility study;

7.3.3 Obtain more human factor information plans

During the study, obtain more information about human factors, screen more suitable population for device treatment, exclude special conditions that may affect the effect of surgery, analyze the obstruction site of enrolled subjects in detail, and select appropriate surgical methods based on overall health;

7.3.4 Organize peer experts to conduct scientific and reasonable discussion and analysis

Ensure correct interpretation of inclusion and exclusion criteria, and organize peer experts to conduct scientific and reasonable discussion and analysis on the conditions that may affect diseases and successful surgery that are not clearly listed in inclusion and exclusion criteria;

7.3.5 Retrospective analysis of data of each follow-up point

Regular follow-up that is more frequent than traditional feasibility or key study. Retrospective analysis of data of each follow-up to monitor subject safety and equipment effectiveness in real time;

7.3.6 Retrospective systemic summary analysis of AEs

Regular reporting of AEs rather than each occurrence and retrospective systemic summary analysis of each AE;

7.3.7 Detailed field records of every use of device

Detailed field records of every use of device. Report performance parameters of the equipment after use, which can help to determine whether the equipment runs as expected;

7.3.8 Detailed analysis of every enrolled subject whose surgery is successful

Whether every enrolled subject whose surgery is successful has anatomical characteristics that are beneficial for operation of device? If it only meets the qualification requirements but does not have such special anatomical characteristics, may it increase the difficulty of using the equipment? Screen more suitable population for device treatment and exclude special conditions that may affect the surgery effect.

7.4 Parameters of safety evaluation

Safety analysis: Safety analysis is based on safety analysis set (SS).

For both safety evaluation and device defect evaluation, statistical description method is adopted to describe AEs (or SAEs), device-related AEs (or SAEs), type, number of cases and incidence of device defects, and list the type, frequency, severity and relationship with study device of AEs that occurred in this trial.

7.5 Calculation of sample size

This study is an exploratory study aiming to investigate the effectiveness and safety of the product, so sample size is not calculated. It's expected that 10 subjects are included to resect ventricular septal myocardial tissue through apex of the heart by myocardial resection system under the guidance of ultrasound.

7.6 Significance level and power of clinical trial

This study is an exploratory pre-trial without significance level or power.

7.7 Expected drop-out rate

This study is an exploratory pre-trial without expected drop-out rate.

7.8 Qualified/unqualified criteria of clinical trial results

This study is an exploratory study aming to investigate the effectiveness and safety of the product, so qualified/unqualified criteria are not set.

7.9 Criteria and reasons for terminating the test based on statistical reasons

This study has no interim analysis and doesn't terminate based on statistical reasons.

7.10 Statistical method of all data, including treatment of unreasonable data, such as missing, unused or wrong data (including drop out and withdrawal)

After the database is locked, perform statistical analysis and logic testing according to statistical analysis plan, and provide a statistical analysis report according to the results.

- **Treatment of missing values**: Missing value will not be imputed in principle. Specific treatment method will be clarified in detail in the statistical analysis plan.
- **Treatment of unreasonable data**: In the process of data management, the data will be checked logically. If unreasonable data are found, the investigator or data entry staff will be queried, and the database can be locked until all unreasonable data are resolved.
- **Treatment of wrong data**: In the process of data management, quality management of data will be performed. If wrong data are found, the investigator or data

entry staff will be queried until all wrong data are corrected, then data management will be performed.

7.11 Procedures of reporting deviation from statistical plan

In case of "incomplete implementation of statistical analysis plan", the change procedure shall be applied in advance, and changes of the statistical plan shall be recorded in the statistical analysis plan, including changes in location, reason and time. Protocol deviations shall be reported by the investigator to the hospital organization office and Ethics Committee.

7.12 Criteria and reasons of subjects included in the analysis

This clinical trial has three statistical data sets, ie. full analysis set (FAS) and per protocol set (PPS) for safety analysis, and safety set (SS) for safety analysis.

- FAS: According to intention-to-treat (ITT) principle, all subjects who are enrolled and use the device and receive at least one effect evaluation.
- PPS: A sub set of FAS, includes subjects who don't violate main inclusion/exclusion criteria, have good compliance, don't have any protocol violation that affects main efficacy parameters.
- SS: All subjects who participate in the trial, use the study device and receive at least one safety evaluation.

7.13 Exclusion of special information and reasons (if applicable) in hypothesis testing

None.

8 Data Management

8.1 Management of database

Paper CRF is used to collect data in this trial. Data management will be performed in accordance with the principles of Technical Guidelines for Clinical Trial Data Management to ensure integrity, accuracy, authenticity and reliability of clinical trial data.

8.2 Permission assignment

The system administrator grants different permissions according to different roles of data-entry staff, data administrator, (principal) investigator and clinical monitor. Data-entry staff has the authority to enter, modify, browse and answer queries. Investigator has the authority to enter, modify, browse and answer queries. Besides the authority of the investigator, Principal Investigator has the authority of signature. The monitor has the authority to browse, send/close queries and check original data. Data administrator has the authority to browse, send/close queries, review, lock data and lock authority.

8.3 Data entry

Clinical investigator or the data-entry staff (clinical coordinator) designated by the investigator shall enter source data into CRF timely and accurately.

During the study, the study site shall store original record of each subject, including study medical records, laboratory data and any other examination and evaluation results as well as visit records, basic information and medical information of the subject and also original copy of the informed consent signed by the subject, so as to obtain relevant original data necessary for CRF. Field monitor can inspect to validate at any time.

8.4 Design and establishment of database

The database is established by the data management department and shall comply with FDA 21 CFR Part 11. The database shall be used to manage system login, data entry, modification, deletion and other data traces. For establishment of the database, it is necessary to adopt or refer to CDISC standard.

8.5 Sending and solving of query

After entry into the Electronic Data Capture (EDC) database, the system will check the data as per the data check plan (edited logic check), and issue the request of system query for questioned data. Clinical monitor and data administrator check the data manually, and send manual queries of questioned data to the EDC database. Data-entry staff or the investigator confirms and answers manual query and system query, and modifies wrong data if necessary until the query is resolved. If the answer fails to resolve the query, the data administrator and clinical monitor can query the data again, and all records are saved in the EDC database.

8.6 Modification and review of data

Data-entry staff or the investigator can modify the data after check, and fill the reasons for modification in the CRF. Principal Investigator has the authority to sign all final data.

8.7 Edit check

Edit of data includes computerized edit check, manual check (medical check, statistical check) and data check meeting. The investigator or designated staff shall correct or clarify inconsistent data (Data Query) found in the check process timely.

8.8 CRF signature

The monitor and data administrator check the data in the database, after that, Principal Investigator will confirm the authenticity and integrity of data and sign.

8.9 Locking and export of database

After all data are reviewed, the data administrator will lock the database according to the database locking protocol. After all data are accurately entered into the database, Principal Investigator, the Sponsor, clinical monitor, data administrator and statistical analysts will hold a data review meeting to report the project and discuss existing problems. After all the problems are resolved, the data administrator can start database locking after confirming that all parties have no questions. After all data are entered into the EDC accurately, the monitor checks all original data, the data administrator reviews all data, Principal Investigator signs all data electronically, and the database can be locked upon approval.

In case of any modification after the database is locked, an application shall be submitted, and database unlocking and modification can be performed only after the Sponsor, investigator, data-entry staff, monitor and data administrator discuss and sign for confirmation.

8.10 Archive

CRF will be archived as required at the end of study. Clinical study site will store clinical trial materials for 10 years after end of study.

Safety and environmental issues shall be considered for archiving. No study documents shall be destroyed without written permission of the investigator.

9 Feasibility Analysis

9.1 Feasibility analysis of success

1) The ultrasound-guided transapical approach is widely applied, such as repair or replacement of aortic valve and mitral valve. The technique is mature, and its safety and reliability have been verified in clinical practice. For this trial, a new cardiac resection device is used for tissue resection through a new surgical approach at the apex of the heart. This approach doesn’t need chest or extracorporeal circulation, can evaluate obstruction level and modify surgical field in real time, and dredge LVOTO through multiple resections. Feasibility and safety of this approach have been verified in porcine trial. Therefore, it is expected that the investigational product can meet the requirements of clinical trials with reliable safety performance and sufficient countermeasures of surgical risk in the apical approach.

2) This clinical trial is conducted by professional hospitals and investigators with qualification of clinical trial. The investigators have rich experiences of clinical practice, receive CGP training, provide treatment as per the clinical trial protocol and advise the subject to comply with medical advice.

9.2 Feasibility analysis of failure

Conduct of this trial does not comply with trial protocol, the use instructions or precautions, all observation results in the clinical trial are not complete, and lack of original data and other factors may cause the trial to fail.

There may also be other unpredictable risks in this study, such as poor physical constitution, severe allergies, disease worsening, accidents and unpredictable events during the trial, which may lead to study failure. However, the risk can be minimized by complying with this protocol, participating in clinical study at the specified study site, complying with inclusion criteria, and closely monitoring the physical condition of subjects during the study and/or follow-up.

The investigator shall record all AEs and device defects found during the clinical trial, and analyze the reasons of AEs together with the Sponsor.

9.3 Potential risks and benefits

9.3.1 Prediction of AEs and measures

Possible intraoperative or postoperative AEs of surgery guided by minimally-invasive myocardial revascularization system ultrasound navigation mainly include arrhythmia, mitral valve injury, aortic valve injury, pericardial effusion, stroke, ventricular septal defect and hemorrhagic shock as follows:

- **Arrhythmia**

When the hypertrophic tissue of ventricular septum is resected, the atrioventricular conduction system of the heart running in ventricular septum may be damaged due to tissue resection. Arrhythmia includes atrioventricular block, left bundle branch block, atrial fibrillation.

It is necessary to enhance the investigator's training, improve the proficiency of investigator, define non-injurable myocardial resection range, enhance monitoring of intraoperative rhythm, observe ECG change when myocardial tissue is resected and provide appropriate and timely treatment if persistent severe arrhythmia occurs. Asymptomatic patient who has first-degree or mild second-degree atrioventricular block doesn't need treatment, and implantation of a pacemaker is necessary for complete atrioventricular block. Asymptomatic patient who has left bundle branch block doesn't need treatment, and cardiac resynchronization therapy can be performed for complete left bundle branch block. Anticoagulant therapy can begin for patient whose atrial fibrillation is graded as high-risk embolism, and drug or electric cardioversion and catheter ablation are prepared.

- **Mitral valve injury**

When the myocardial resection system enters the left ventricle through the apex under the guidance of ultrasound, location of resected tissue may cause mitral valve injury. It is necessary to enhance the investigator's training, improve the proficiency of the investigator, and understand cardiac anatomical marker under ultrasound. This can reduce mitral valve injury effectively. In case of intraoperative mitral regurgitation or worsening of mitral regurgitation, the investigator shall determine no treatment, mitral valve repair or mitral valve replacement according to mitral valve injury and regurgitation.

- **Aortic valve injury**

When the myocardial resection system enters the left ventricle through the apex under the guidance of ultrasound, location of resected tissue may cause aortic valve injury.

It is necessary to enhance the investigator's training, improve the proficiency of the investigator, understand cardiac anatomy, and modify according to the patient's actual condition. This can reduce aortic valve injury effectively. For mild aortic valve injury (reflux per stroke showed by apical ultrasound), special treatment is unnecessary; aortic valve repair can be performed for severe injury; and aortic valve replacement can be performed for irreparable injury.

- **Pericardial effusion**

Pericardial effusion may be caused by postoperative incision effusion and apical tear. Dyspnea is the most common symptom of pericardial effusion. A large amount of pericardial effusion can cause pericardial tamponade, and the syndrome of hypotension, low heart murmur and jugular vein distension will occur.

It is necessary to enhance the investigator's training. Careful operation and tight suture for apical closure ensure suture. Accurate determination of the cause of pericardial effusion is critical.In case of pericardial effusion, emergent pericardiocentesis is necessary to relieve symptoms of pericardial tamponade. It is necessary to define the primary cause of pericardial effusion and treat the primary disease.

- **Stroke**

Postoperative atrial fibrillation causes thrombosis. When the thrombus flows through the aorta and carotid artery through the internal cerebral artery, cerebral artery embolism may occur, even leading to ischemic stroke.

Monitor the patient's ECG after surgery. Patients with atrial fibrillation who have a high risk of thrombus shall take anticoagulant drugs as soon as possible and take medicine or electric cardioversion. Patients whose conditions permit can receive radiofrequency catheter

ablation.

- **Ventricular septal defect**

Myocardial resection system aspirates myocardial tissue in the negative-pressure tube by negative pressure, ultrasound imaging is unclear, and aspiration of over tissues may cause ventricular septal defect. Small area of ventricular septal defect and less left-to-right shunt have few effect on the patient's daily activities; large area of ventricular septal defect and more left-to-right shunt can cause systemic ischemia and symptoms of pulmonary congestion.

Evaluate ventricular septal hypertrophic tissue before surgery, and perform careful operation and rotary resection of target hypertrophic tissue. The ventricular septal defect found during surgery can be repaired at the same time.

- **Hemorrhagic shock**

There is a risk of blood loss at the purse-suture during and after the apical approach. Hemorrhagic shock will occur when rapid blood loss accounts for 30-35% of total blood.

Enhance the investigator's training, and perform careful operation. Identify abnormal bleeding and bleeding site, and perform emergent hemostasis.

For above risks, effective measures can be taken to minimize risks. Specific measures are as follows:

1. The investigator with rich experience of cardiac surgery via apical approach is selected. After training, the investigator resects ventricular septal myocardial tissue with the myocardial resection system via apical approach under the guidance of ultrasound according to SOP;

2. The investigator controls the subject's inclusion/exclusion criteria strictly;

3. Follow the subject after surgery via apical approach under the guidance of ultrasound, and provide the subject with the follow-up card, including contact of the investigator and postoperative precautions. The subject can contact and consult with the investigator in case of any discomfort at any time, or return to the hospital for examination and treatment according to the investigator's determination. The subject will be monitored closely during following up. In case of any unpredictable risk, the investigator will provide proper and reasonable medical treatment timely according to the subject's condition.

9.3.2 Benefits

The subject does not need to pay relevant tests during this clinical study, including vital signs, physical examination and laboratory examination. During the trial, the subject can receive good medical services and the disease will be diagnosed;

Important information obtained from this study may provide information to patients and healthcare providers who will use such devices in future, and help to increase their own or other patients' treatment options.

10 Quality control of clinical trial

10.1 Selection of clinical sites and investigators

The Sponsor will select qualified investigators who have received unified training for this study, have experience and have legal right to conduct clinical study to participate in this clinical trial. Selection of study site will be based on recent review results of study sites and comprehensive ability of the principal investigator in the study site.

10.2 Training

10.2.1 Training in study site

All investigators/study staff must participate in the training provided by the Sponsor. The training can be conducted in the form of investigator meetings, initiation visits of the study site or other appropriate forms. Telephone training can also be conducted if necessary. The contents of training for investigators/study staff include, but are not limited to, study protocol, CRF filling, responsibilities of study staff and training of SOP for surgery. All trained investigators/study staff must sign a training log (or similar form) after receiving the training. Before signing the training log, investigators/study staff shall not engage in any work related to the trial that is beyond the scope of the treatment standard of the study site.

10.2.2 Training of the Sponsor/monitor

The Sponsor and/or the designated monitor will receive training on the use of relevant protocol, CRF and medical devices (if applicable), and the training process will be recorded according to written procedures.

10.3 Monitoring of clinical trial

10.3.1 Designate monitor

The trial monitor is the person specially responsible for monitoring the trial progress. The monitor shall be appropriately trained and qualified to monitor the progress of clinical study. The Sponsor can designate the additional monitor at any time during the trial. For other information about the staff in charge of monitoring, please contact the Sponsor.

10.3.2 Visit

Before the trial starts, the Sponsor's monitor (or representative) will visit the

investigator to ensure that the following standards are met:

The investigator understands and accepts the obligation to conduct clinical trials in accordance with the study protocol and applicable laws and regulations, and signs clinical trial agreement;

The investigator and staff have sufficient time and facilities to conduct the study, and can contact a sufficient number of appropriate subjects to conduct the study;

There must be original data to prove the appropriateness of informed consent procedure, compliance with study protocol, adequate reporting and follow-up of AEs, accuracy of data collected by CRF and device information. The investigator/study site will allow access to these records. The study site shall keep the signature log of monitor visit. The investigator agrees to take sufficient time to cooperate with the monitoring process, and the investigator and/or study coordinator shall be present during monitoring visit. The investigator shall provide an appropriate working environment for the monitor to review relevant documents.

11 Ethical issues of clinical trial and informed consent

11.1 Ethical considerations

11.1.1 Ethics and regulations

This trial complies with Helsinki Declaration, Good Clinical Practice of Medical Device and relevant national regulations.

11.1.2 Medical Ethics Committee

Before the clinical trial, the investigator submits the study protocol, informed consent form (ICF) and other relevant documents to the Ethics Committee (EC) of the hospital where the study site is located. The clinical trial can only be started after approval by EC. Any modification of the study protocol must be approved by EC before conduct. SAEs during the clinical trial shall be submitted to EC in written format timely.

11.2 Informed consent process and text of informed consent

Before enrolling for this study, the investigator must explain the details of the clinical trial to the subject or his/her guardian, including the nature, purpose and expected efficacy of the trial as well as possible AEs and countermeasures, and answer relevant questions raised by the patient. Subjects can be included only after they fully understand the trial and sign the informed consent. The informed consent shall be signed by the investigator, the subject or his/her guardian in duplicate, with each party keeping one copy.

12 Requirements of reporting AEs and device defects

12.1 AEs

12.1.1 Definition of AEs

AEs refer to adverse medical events that occur during the clinical trial, regardless of whether they are related to the medical device used in the trial. The following events are included:

All events related to the study device or control device;

All events related to the study process (all procedures in the clinical study plan);

Other AEs.

12.1.2 Determination of severity of AEs

Observe the process, severity, treatment and outcome of AEs and fill in the AE report form.

According to the following criteria, the severity of AEs can be classified into mild, moderate and severe.

Mild: It does not affect the treatment and the time of admission and discharge, requires no special treatment, and has no significant impact on the health and daily life of the subject.

Moderate: It needs special treatment and has adverse impact on the health and daily life of the subject.

Severe: It causes death or serious worsening of health, including fatal disease or injury, permanent defect of physical structure or function, need for hospitalization or extension of hospitalization, need for medical or surgical intervention to avoid permanent defect of physical structure or function.

12.1.3 Relationship between AEs and the device

According to 6 documents including Application and Approval Form for Ethical Review of Clinical Trials of Medical Devices issued by NMPA (No. 58, 2016), the relationship between AEs and medical devices is considered based on:

① Definitely related: belonging to the AEs caused by the used product, the AE has reasonable time sequence, occurs during intraoperative use, is not a common AE of the surgery, can not be explained by other reasons or the subject's current disease;

② Probably related: The AE, a known type of reactions of the used product, has reasonable time sequence, can not be explained by other reasons, is a intraoperative AE, is not a common AE of the surgery, and can not be explained by the subject's current disease;

③ Possibly related: The AE, a known type of reactions of the used product, has reasonable time sequence after treatment, is a perioperative AE, is not a common intraoperative AE of the surgery, and can not be explained by other reasons or the subject's current disease;

④ Possibly unrelated: The AE, a known type of reactions of the used product, has reasonable time sequence after treatment, can be explained by other reasons, **is not a perioperative AE**, can be explained by the subject's current disease;

⑤ Definitely unrelated: The AE, not a known type of reactions of the used product, doesn't have reasonable time sequence after treatment, can be explained by other reasons, **is not a perioperative AE**, and can be explained by the subject's current disease;

- **Evaluation criteria of the relationship between AEs and the device**

	Definitely related	Probably related	Possibly related	Possibly unrelated	Definitely unrelated
Has reasonable time sequence	Y	Y	Y	Y	N
Type of device defect and AE	Y	Y	Y	Y/.N	N
Common AE of the surgery	N	N	Y/N	Y/.N	Y
Time of the AE	Intraoperative use	Intraoperative	Perioperative	?	Not perioperative
Explained by other reasons	N	N	Y/N	Y	Y
Explained by the subject's current disease	N	N	Y/N	Y/.N	Y

Note: Y, yes; N, no; Y/N, difficult to be yes or no; ?, unclear

12.1.4 Record of AEs

All AEs that occur during the study must be truthfully recorded in the AE table. The investigator shall provide treatment and follow-up services for the AE until the symptoms disappear or stabilize, and analyze the cause of the event together with the Sponsor. The investigator shall make a preliminary judgment on AEs, which can be basically classified into intraoperative AEs, extra-treatment AEs and post-treatment AEs. AE is the adverse medical event that occurs during the clinical trial, regardless of the relationship with the study medical device.

12.2 SAEs

SAE is the event that occurs during the clinical trial and causes death or serious

worsening of health, including fatal diseases or injury, permanent defect of physical structure or functions, need for hospitalization or extension of hospitalization, medical or surgical intervention to avoid permanent defect of physical structure or functions; events that lead to fetal distress, fetal death or congenital abnormality or defect.

12.3 Device defects

Device defects refer to unreasonable risks that may endanger human health and safety during normal use of the medical device during the clinical trial, such as label error, quality problem and malfunction.

12.4 Relationship between AEs and device

The investigator shall determine whether the medical device can cause AEs or be a factor of AE. The conclusion must be recorded in appropriate CRF. The investigator shall evaluate the temporal relationship, correlation with underlying disease and whether there is a more reasonable reason before making a judgment.

12.5 Reporting procedure and contact information

12.5.1 Reporting procedure of SAE

When SAEs occur during the clinical trial, the investigator shall immediately take appropriate treatment measures for the subject, report in writing to the authority about the clinical trial of medical device at the clinical site, and notify the Sponsor in writing. The authority of clinical trial of medical device shall report in writing to appropriate Ethics Committee and the drug administration departments and health authorities at the levels of provinces, autonomous regions and municipalities directly under the Central Government. Clinical site and the investigator shall provide all necessary information of death case to Ethics Committee and the Sponsor.

12.5.2 Reporting procedure of device defect

The investigator shall record device defects found during the clinical trial, analyze the cause together with the Sponsor, write a written analysis report, put forward suggestions on continuing, suspending or terminating the trial, and submit it to the Ethics Committee for review by the management of clinical trial of medical device at the clinical site.

For SAEs and device defects that may lead to SAEs, the Sponsor shall report to the drug administration and the same level of health authorities within 5 work days after being informed, and shall also report to other clinical sites and investigators participating in the trial, and notify the Ethics Committee of the clinical site in time through the authority of clinical

trial of medical device.

13 Clinical study protocol deviation and revision of clinical study protocol

13.1 Clinical study protocol deviation

The investigator shall not change or deviate from the study protocol, except in an emergency to protect the subject's life and safety. If the investigator deviates from the test protocol in order to protect the subject's life and safety in an emergency, he/she shall notify the Sponsor and the Ethics Committee (if applicable) of the deviation and those deviations that affect the scientific nature of the clinical study.

All protocol deviations, causes and date must be recorded and reported to the Sponsor. The Sponsor will review and evaluate these protocol deviations and take necessary corrective and preventive measures timely, including but not limited to informing the site to retrain or close the site. Specific protocol deviations can include, but are not limited to, the following types:

Included subject doesn't meet the inclusion/exclusion criteria;

The subject doesn't (or accurately) receive trial and/or test required in the clinical study protocol;

The investigator doesn't report AEs or device defect within a period required by the clinical study protocol;

The subject is included when the Ethics Committee's approval is invalid.

13.2 Requirements of revision of clinical study protocol

Generally speaking, the clinical study protocol shall be strictly implemented after being approved by the Ethics Committee. If it is necessary to supplement or revise the study protocol after the study starts, the investigator and the Sponsor should revise it after agreement and submit it again to the Ethics Committee for approval before implementation. Modification of the study protocol shall be recorded in detail, including specific contents and reasons of the modification, communication letter submitted to the Ethics Committee for re-approval and approval document of the Ethics Committee.

14 Direct access to source data and files

The investigator/site will allow relevant personnel to directly access original data/information related to the trial to cooperate with the monitor, check, evaluation of the Ethics Committee and inspection of the regulatory authority 啥，又是动词 又是名词的.

When the subject signs the informed consent, it means that the Sponsor or its designated

staff is allowed to review the information in the medical record that is related to the trial. As a part of the informed consent, the investigator will obtain the permission of the subject to allow the monitor or regulatory authority to review any record with the subject's identity in the clinical trial at the study site, but it must be kept confidential. These information can be shared with regulatory authority. However, the Sponsor shall not disclose personal and private information of the subject in other ways according to the local laws of data protection.

15 Finance and insurance

All parties in this clinical study will sign a written agreement with the clinical site, which will specify the finance and payment of this clinical trial in detail. For details, see the agreement signed by the parties.

All parties promise to bear the treatment cost and corresponding economic compensation for the subject who suffers from injury or death related to the clinical trial, except for damage caused by the fault of the clinical site and healthcare staff in diagnosis and treatment activities.

16 Coverage of the clinical trial report

The investigator shall verify the safety and effectiveness of the medical device used in the trial according to the design requirements of the clinical study protocol, and complete the clinical trial report. The clinical trial report shall be consistent with the clinical study protocol. The clinical trial report shall be signed and dated by the investigator, reviewed, dated and sealed by the administration of clinical trial of medical device at the clinical site, and then submitted to the Sponsor.

17 Confidentiality

17.1 Confidentiality statement of the protocol

This protocol is used to guide the clinical trial in which drugs via apex approach delivered by minimally-invasive myocardial rescetion system under guidance of ultrasound can not control hypertrophic obstructive cardiomyopathy with symptoms of left ventricular outflow tract obstruction. The included information is confidential and shall not be disclosed to any third party.

17.2 Confidentiality statement of study materials and information

The study site shall keep all materials and information that are obtained, but not limited to performance structure, trial data, reports and results related to the subjects confidential. The records obtained from this trial will be submitted to the Sponsor and relevant drug

administration for review. These data may also be submitted to the health authorities of other countries that may approve this product for reference. The results of the trial may be published in academic meetings or journals, but the privacy of the subjects will never appear in the information published above.

18 Publication agreement of trial results

18.1 Publication of trial results

A separate publication plan that is periodically updated will be issued based on the study progress.

18.2 Conditions for publication

1) The sponsor agreement must be signed before publication;

2) If co-investigators participating in this study belong to the same site, only the principal investigator of the site can designate the name of the person who is in the authorship (principal investigator and co-investigator);

3) The number of co-authors in the authorship shall meet specific requirements of each journal;

4) The name of the Sponsor shall be quoted in all publications, and at least one project team member in the main author list is from the Sponsor.

Any designated author shall meet all the criteria that the following authorship should meet:

Has made great contributions to the idea or design of this work or to data acquisition, analysis or summary;

Compile or strictly revise this work for important knowledge content;

Final approval of the version to be published;

Sign an agreement, be responsible for all aspects of the work, and ensure that problems related to the accuracy and completeness of the work can be appropriately handled and explained.

19 Responsibilities

19.1 Responsibilities of Ethics Committee

The Ethics Committee of the clinical study site of medical device shall consist of at least five members, including medical professionals and non-medical professionals, male or female. Non-medical professional members consist of at least one legal worker and one person outside the clinical study site. Members in the Ethics Committee shall have the

qualification or experience of evaluating scientific, medical and ethical aspects of this clinical trial. All members shall be familiar with the ethical principles and relevant regulations of clinical trials of medical devices, and comply by the regulations of the Ethics Committee.

The Medical Device Ethics Committee shall comply with the ethical principles of Helsinki Declaration of the World Medical Congress and the provisions of drug regulatory authority, establish corresponding work procedures, formulate documents, and perform its duties in accordance with the work procedures.

Members of the Ethics Committee who are independent of the investigator and the Sponsor have the right to express their opinions and participate in the voting of the relevant trials.

The Ethics Committee shall issue a notice before the meeting. The number of participants in review and voting shall be no less than 5. Any decision shall be passed by more than half of the members of the Ethics Committee.

The investigator can provide information about any aspect of the trial, but shall not participate in the review, vote or express opinions.

When reviewing some special trial, the Ethics Committee may invite experts in relevant fields to participate.

The Ethics Committee shall strictly review the study protocol and relevant documents to safeguard the subject's rights and interests, and shall focus on the following contents:

1) The investigator's qualification, experience and whether he/she has sufficient time to participate in the clinical trial;

2) Whether the staffing and equipment conditions of the clinical study site meet the requirements;

3) Whether the risks of the subject are proportional to the expected benefits;

4) Whether the study protocol considers ethical principles and conforms to scientific nature, including whether the study purpose is appropriate, whether the subject's rights and interests are protected, whether other people may be protected from risks, and whether the selection method of the subjects is scientific.

Method of selecting subjects:

1) Whether the information about the trial provided to the subject or his/her guardian is complete, whether the subject can understand it, and whether the method of obtaining the informed consent is appropriate;

2) If necessary, the Ethics Committee shall organize the representatives of the subject population to test the comprehensibility of data, evaluate whether the informed consent is

appropriate, and evaluation results shall be recorded in writing and kept for 10 years after the end of the clinical trial;

3) Whether the treatment and insurance measures are adequate if the subject suffers injury or death related to the clinical trial;

4) Whether the modification on the study protocol is acceptable;

5) Whether the possible harm to the subject can be analyzed and evaluated regularly during the clinical trial;

6) Protocol deviations may affect the subject's rights, interests, safety and health, or affect the scientificity and integrity of the trial, and whether it is acceptable.

In order to ensure consistent and timely review, the Ethics Committee of the leading institution shall establish the work procedure of collaborative review for ethical review of multi-center clinical trial. The Ethics Committee of the leading clinical study site shall review the ethical rationality and scientificity of the study protocol before the trial. On the premise of accepting the review opinions of the leading clinical study site' Ethics Committee, the Ethics Committees of other clinical study sites can review the feasibility of this trial in the clinical study site in the form of meeting review and document review, including qualification and experience of the investigator, equipment and conditions. Generally, the study protocol will not be modified, yet the trial in the clinical study site can be refused.

After receiving the application for clinical trial of medical devices, the Ethics Committee shall convene a meeting to review and discuss, issue written comments, seal, and attach a list of persons attending the meeting, specialty and personal signature.

The opinions of the Ethics Committee include:

1) Agree;

2) Agree after necessary modification;

3) Not agree;

4) Suspend or terminate approved trial.

The Ethics Committee shall follow and supervise the clinical trial in the clinical study site, and may request in writing to suspend or terminate the clinical trial at any time in case of any situation where the subject's rights and interests cannot be guaranteed.

The suspended clinical trial shall not be resumed without the consent of the Ethics Committee.

The Ethics Committee shall keep all relevant records for at least 10 years after completion of the clinical trial.

19.2 Responsibilities of the Site

The clinical site shall evaluate relevant resources according to the characteristics of the medical device used in the trial to determine whether to accept the clinical trial before accepting the clinical trial by the clinical study site. The clinical trial site shall keep clinical trial records and basic documents appropriately according to the agreement with the Sponsor.

The investigator responsible for the clinical trial shall meet the following conditions:

1) Associate chief physician, associate professor, associate investigator and other relevant professional and technical titles and qualifications of working in the clinical study site;

2) Expertise and experience required for the medical device, and relevant training if necessary;

3) Be familiar with information and reference related to the clinical trial required and provided by the Sponsor; Have the ability to coordinate, control and use persons and equipment in the clinical trial, and handle AEs caused by the study medical device and other relevant events;

4) Be familiar with relevant laws, regulations and the present protocol.

5) Clinical study site and the investigator shall ensure the authenticity, accuracy, clarity and safety of the data, documents and records formed in the clinical trial.

6) Clinical study site and the investigator shall accept the monitoring and inspection of the Sponsor and the supervision of the Ethics Committee, and provide all necessary records related to the trial. If the drug administration and health authority send inspectors to carry out the inspection, the clinical trial site and the investigator shall cooperate.

7) When the clinical trial site and the investigator find that risks overweigh the possible benefits, or have obtained the results sufficient to judge the safety and efficacy of the study medical device, and need to suspend or terminate the clinical trial, they should notify the subject, and ensure that the subject receives appropriate treatment and follow-up services, and provide detailed written explanations as required. If necessary, report to local drug administration of the province, autonomous region, or municipality directly under the Central Government. When receiving the notice from the Sponsor or the Ethics Committee that the clinical trial needs to be suspended or terminated, the investigator shall promptly notify the subject and ensure that the subject receives appropriate treatment and follow-up services.