The Effectiveness and Safety in the treatment of CPVI for Symptomatic Paroxysmal Atrial Fibrillation with THERMOCOOL® SMARTTOUCH™ Catheter in China—A Multi-center Clinical Registry Study

SMART CHINA

Protocol No: BW-201501

Version 2.0

Jan 07, 2016

Amendment Record

Version No.	Eff.Date	Original Content	Modified Content
V2.0	Jan7,2016	6 months enrollment period and follow-up at 3, 6, 9 and 12 months after CPVI. Blanking period will span 90 days after CPVI in Protocol Summary	9 months enrollment period (adjust the progress according to the actual status) and follow-up at 3, 6, 9 and 12 months after CPVI. Blanking period will span 90 days after CPVI in Protocol Summary
		Transesophageal Echocardiogram (TEE) – performed within 24 hours prior to the AF procedure in Section 5.3	To detect LA thrombi, e.g. routine TEE (Transesophageal Echocardiogram) on the day or the day before AF ablation in Section 5.3
		TEE and the 1st remark in 5.8 (Data Collection flow chart)	"TEE" is changed to "Examination to detect LA thrombi"; the 1st remark is changed to "1. To detect LA thrombi, e.g. routine TEE on the day or the day before AF ablation" in 5.8 (Data Collection flow chart)

Signature Page:

Study Title: The Effectiveness and Safety in the treatment of CPVI for Symptomatic Paroxysmal Atrial Fibrillation with THERMOCOOL® SMARTTOUCH™ Catheter in China——A Multi-center Clinical Registry Study (SMART CHINA)

Study No.: BW-201501

Version No.: 2.0

Date: 2016-01-07

I confirm that I have read this protocol; I understand that I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for Good Clinical Practices, or the applicable laws and regulations of the study site in China for which I am responsible, whichever provides the greater protection of the individual.

I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the device and the conduct of the study.

I agree to maintain all study related information supplied by JJMS in strictest confidence. When information regarding this study is submitted to an independent ethics committee it will be forwarded with a requirement that all study related material is to be held strictly confidential.

_____ _____

Investigator's Signature Date

_____

Investigator's Name (Print or Type)

Professor

Investigator Title

_____

Name of Facility

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The Effectiveness and Safety in the treatment of CPVI for Symptomatic Paroxysmal Atrial Fibrillation with THERMOCOOL® SMARTTOUCH™ Catheter in China——A Multi-center Clinical Registry Study (SMART CHINA)

Protocol Summary

Title:	The Effectiveness and Safety in the treatment of CPVI for Symptomatic Paroxysmal Atrial Fibrillation with THERMOCOOL® SMARTTOUCHTM Catheter in China——A Multi-center Clinical Registry Study (SMART CHINA)
Design:	This is a prospective, multicenter, non-randomized clinical evaluation utilizing the THERMOCOOL® SMARTTOUCH™ catheter undergoing CPVI compared to a pre-determined performance goal.
Purpose:	The purpose of this study is to assess the effectiveness and safety of the THERMOCOOL® SMARTTOUCH™ catheter in the treatment of drug refractory symptomatic paroxysmal atrial fibrillation (PAF) undergoing CPVI.
Enrollment:	Approximately 200 patients will be enrolled (minimum 188).
Clinical Sites:	Up to 15 sites in China.
Study Duration:	9 months enrollment period (adjust the progress according to the actual status) and follow-up at 3, 6, 9 and 12 months after CPVI. Blanking period will span 90 days after CPVI.
Study Population:	Subjects with drug refractory symptomatic PAF who have had at least one (1) AF episode in the 12 months prior to enrollment and have failed at least one antiarrhythmic drug (AAD).
Primary Endpoint:	The primary effectiveness endpoint for this study is freedom from documented symptomatic atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL) episodes through 12-month follow-up after the index CPVI procedure.
Secondary Endpoints:	Acute success rate at 0.5h post CPVI (entrance block after CPVI are achieved in all veins with an isoproterenol intravenous challenge) CF and Force Time Integral (FTI) for index procedure by PV segments (from PV to the atrium, divided into 3, 6, 9 and 12 point positions)

Number, percentage and sites of Pulmonary vein(PV) reconnection after index procedure(from PV to the atrium, divided into 3, 6, 9 and 12 point positions)

Total procedural, ablation time and fluoroscopy time

The incidence of AEs related with the procedure and study catheter

List of Acronyms/Abbreviations and Study Terms/Definitions

Acronym/Abbreviation	Expanded Term
AAD	Antiarrhythmic Drug
ACC/AHA/ESC	American College of Cardiology/American Heart Association/European Society of Cardiology
AE	Adverse Event
AF	Atrial Fibrillation
AT	Atrial Tachycardia
CABG	Coronary artery bypass graft surgery
CRF	Case Report Form
CVA	Cerebrovascular Accident or Stroke
EC	Ethics Committee
ECG	Electrocardiogram
EP	Electrophysiology
GCP	Good Clinical Practices
HM	Holter Monitoring
HRS/EHRA/ECAS	Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
IFU	Instructions For Use
LA	Left Atrium
LV	Left Ventricle
MI	Myocardial Infarction
PAF	Paroxysmal Atrial Fibrillation
PI	Principal Investigator
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
RA	Right Atrium
RF	Radiofrequency
RV	Right Ventricle
SAE	Serious Adverse Event
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiography
UADE	Unanticipated Adverse Device Effect

1.0 Introduction

1.1 Background

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1.2 Rationale

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1.3 Device Description

The commercially available THERMOCOOL" SMARTTOUCH'" catheter Diagnostic /Ablation Deflectable Tip Catheter with Contact Force Sensing Capability is the only study catheter to be used in this study.

The catheter is a multi-electrode luminal catheter with a deflectable 3.5 mm tip designed to facilitate electrophysiological mapping of the heart and to transmit RF current to the catheter tip electrode for ablation purposes. The catheter shaft measures 7.5 F with 8.0 F ring electrodes. For ablation, the catheter Is used in conjunction with an RF generator and a dispersive pad (indifferent electrode).

The catheter has force sensing technology that provides a real-time measurement of contact force between the catheter tip and the beating heart wall. It is specifically designed to allow full integration with the electro-anatomic mapping system, which provides both graphical and numerical displays of CF and the force vector in real time; thus both magnitude and direction of the force are visualized via a 3-D vector. This catheter is a modification of the widely used irrigated-tip bidirectional diagnostic/ablation catheter (THERMOCOOL® EZ Steer'", Biosense Webster) and diagnostic/ablation I catheter (NAVISTAR THERMOCOOL'", Biosense Webster), using a similar irrigation and bidirectional system. Only the distal tip has been modified with additional elements to accomplish CF sensing.

The VisiTag™ Module software is a novel algorithm that has been developed, which automatically tags the RF catheter ablation applications on the Carto® 3 Mapping System. Adhesive electrical dispersive pads for the RF current return path and available equipment for recording multiple intra-cardiac electrograms and signals from the RF generator (i.e., power, temperature, impedance) in electrical stimulation will be used.

Study participants who undergo PVI are to have their procedure performed and completed (as described in section 5.4) using the study device in conjunction with the CARTO® 3 System (version 3.2 or higher), an electro-anatomic mapping system for use in performing catheter-based electrophysiological RF ablation procedures. All devices to be used in this study are commercially available, conform to the applicable local regulations and are to be used according to the approved indication and their Instructions for Use (IFU). Each site will be required to have specific equipment for performing RF ablation procedures. Sites will be instructed to refer to the User's Manual / Instructions for Use for the set-up of system / device / component.

1.4 Risk analysis

RF catheter ablation has been used for nearly two decades. The use of saline-irrigated ablation catheter is routine for many PAF ablation procedures whose risks and complications are well understood.

1.4.1 Description and Analysis of Risks

The incremental risk associated with performing RF catheter ablation using the THERMOCOOL® SMARTTOUCH™ catheter, which includes contact force sensing technology, is small relative to that of a standard electrode catheter that does not include this technology. The larger RF lesion size produced with this catheter may increase pain (during the procedure) associated with RF applications and may increase the risk of cardiac rupture. Increased pain, however, can be managed with intravenous analgesics. Additionally, use of the cooled electrode tip catheter may reduce procedural time, fluoroscopy time and increase procedural success by increasing lesion depth and by minimizing thrombus formation, which necessitates repeated removal and re-deployment of the ablation catheter. While the ability to cool the electrode-tissue interface allows the use of higher power than with a conventional 4mm electrode, RF power in the range of 30-40 watts is often adequate. For any given power setting, the power delivered to the tissue is similar to that used with a 4mm electrode.

Radiofrequency current may cause occlusion of a coronary artery, either by direct thermal damage, spasm, or thrombosis. Experience at numerous centers suggests that the risk of coronary occlusion is less than 0.5%.[35,36] Coronary artery occlusion could produce myocardial infarction (MI), angina or death. Should occlusion of a coronary artery occur for any reason, the investigator will attempt to restore coronary blood flow through pharmacological, catheter and/or surgical intervention, as medically indicated.

The application of radiofrequency current close to the AV node or His bundle could damage or destroy the normal AV conduction system, producing complete heart block and requiring implantation of a permanent pacemaker.

A thrombus may form on the ablation electrode during the application of radiofrequency current without any change in impedance. The thrombus might become dislodged and embolize to produce a stroke, MI, or other ischemic injury. The risk of an embolus is reduced by quickly terminating the application of current after an impedance rise, which limits the size of the thrombus on the electrode. Probably the most important aspect of the THERMOCOOL® family of catheters is the near absence or very low likelihood of thrombus formation during RF.

Thrombus formation on the endocardium following ablation may produce an arterial or pulmonary embolus. This risk may be reduced by the use of aspirin (antithrombotic) and/or anticoagulation therapy, at the discretion of the investigator.

Cardiac perforation may result from catheter manipulation or application of radiofrequency current (risk is <1%).[35,36] This may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. Significant hemodynamic compromise can result in neurologic injury or death. An increased risk of cardiac perforation may be associated with the use of a saline-irrigated electrode catheter due to its ability to create a larger, deeper RF lesion. This risk is greatest in a thin walled chamber (i.e., RA, LA, or RV); however, the risk of perforation related to a deep steam pop is reduced if RF energy is not delivered perpendicular to the wall at power above 35 or 40 watts. If the lesion is deeper, the risk of steam pop is higher above 35-40 watts.

Injury to a cardiac valve may result from catheter manipulation or the application of radiofrequency current (risk <1%).[35-37] This may produce valvular insufficiency and possibly necessitate valve replacement surgery.

The application of RF current along the posterior left atrium can result in thermal injury to the esophagus and the formation of an atrio-esophageal fistula. This is a very rare (0.04%) but severe complication of RF ablation that may require surgical intervention or result in permanent impairment.[37] Reducing power at sites in close proximity to and/or avoiding sites directly over the esophagus may reduce the risk of thermal injury.

Injury to the phrenic nerve may occur as a result of RF application in the region of the right pulmonary veins. The reported incidence of phrenic nerve injury varies from 0% to 0.48% when RF energy is used for catheter ablation.[37] Prior to ablation in the region of the RSPV, investigators are encouraged to perform precautionary measures, such as evaluation of proximity to the phrenic nerve and pacing maneuvers.

Radiation exposure during fluoroscopic imaging of catheters may result in an increase in the lifetime risk of developing a fatal malignancy (0.1%) or a genetic defect in offspring (0.002%).[38-40]

The risk of pulmonary AEs (e.g., pulmonary vein stenosis, thrombus and hypertension), associated with an AF ablation procedure targeting the pulmonary veins, is considered small (<4%).[23,41-47]

Other potential complications, which may result from catheter insertion and manipulation as part of the prerequisite electrophysiology study and mapping procedure, include: Allergic reaction to the local anesthetic, sedatives, x-ray dye, heparin, protamine, or other agents administered during the procedure (risk <1%).[48-52] Arterial or venous injury, including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other

sites along the vessels (risk <1%),[35,36] which may produce hemorrhage, hematoma or ischemic injury to an extremity or major organ. Hemorrhage as a result of anticoagulation (risk <0.5%), which may require transfusion.[35,36] Infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%);[35-37] this risk can be minimized by using standard aseptic technique and by the use of antibiotic agents when indicated.

1.4.2 Minimization of Risks

The criteria for subject selection, methods, personnel, facilities, and training that have been specified for this study are intended to minimize the risk to subjects undergoing this procedure. Subjects will be screened carefully prior to enrollment in the study to confirm compliance with the study inclusion and exclusion criteria.

Participating investigators will be experienced and skilled in performing electrophysiology studies, intracardiac mapping, and ablation of AF with the use of the RF ablation catheters. Operators will have >50 AF ablation case per year experience, and before study initiation, they will perform CF-guided ablation in 5 patients to become familiar with CF monitoring and decrease learning curve-associated bias. Procedures will be performed in electrophysiology laboratories, with the assistance of skilled nurses and technicians. The laboratory will contain sufficient resuscitative equipment and facilities to manage any potential complication. Cardiac surgical facilities, as well as a qualified cardiovascular surgeon, will be available during the ablation procedure in the event that surgical intervention becomes necessary.

Ablation procedures with the THERMOCOOL® SMATTOUCH™ catheter will be performed according to the product Instructions for Use, including but not limited to instructions regarding indications and contraindications for using these devices.

1.4.3 Precautions

Invasive electrophysiological evaluation and catheter ablation may impart some degree of risk to the patient. The risk of serious complications is generally related to the severity of cardiac disease. The degree of risk of the electrophysiological and catheter ablation procedures and the potential benefit of the treatment of symptomatic PAF should be determined by a qualified physician. Failure to observe all contraindications, warnings, and precautions, as listed in the Instructions for Use may result in procedural complications. Procedural complications include: cardiovascular injury or perforation with or without cardiac tamponade, pericardial effusion, esophageal fistula, severe PV stenosis, pulmonary embolus, tricuspid regurgitation, MI, bleeding at the catheter insertion site, sepsis, stroke, and death.

1.4.4 Potential Benefit

The direct benefit for patients undergoing radiofrequency catheter ablation is the potential elimination of AF episodes. It is furthermore expected that quality of life will improve and less frequent hospitalization will be required. The information gathered during the conduct of this study may be of benefit in the future for the treatment of patients with atrial fibrillation.

2.0 Study Objective

The purpose of this study is to assess the effectiveness and safety in the treatment for drug refractory symptomatic paroxysmal atrial fibrillation (PAF) subjects with the THERMOCOOL® SMARTTOUCH™ catheter undergoing CPVI.

3.0 Basic Study Design

This is a prospective, multicenter, non-randomized clinical evaluation utilizing the THERMOCOOL® SMARTTOUCH™ catheter undergoing CPVI compared to a pre-determined performance goal. Approximately 200 subjects (minimum 188) will be enrolled at up to 15 sites in the China.

3.1 Screening

All patients considered for a RF ablation procedure for drug refractory recurrent symptomatic PAF should be screened by the investigator or designated member of the research team for study eligibility.

Symptomatic Episode: symptom(s) which is/are concurrent with a documented episode of AF by either ECG, Holter monitor (HM), or TTM. Symptoms may include but are not limited to: palpitations, irregular pulse (eg, tachycardia or bradycardia), dizziness, weakness, chest discomfort, and breathlessness.

3.2 Informed Consent Form (ICF)

Informed consent is mandatory and the informed consent form signed and dated by both investigator and subject must be obtained from all subjects prior to CRF entering in this study. Any modifications to the Patient Informed Consent Form must be approved by JJMS and the IEC . The copy of Informed Consent Form approved by IEC along with the copies of consent forms signed by every subject must be maintained by every investigator in a designated clinical trial master file. A signed copy of the consent form must be given to each subject. It is the investigator's responsibility to ensure that the Informed Consent process is performed in accordance with GCP.

3.3 Number of Centers

Up to 15 sites in China will participate in this study. Total enrollment among all sites of up to 200 subjects is expected. Sites participating in this study will be selected based upon their capabilities to successfully carry out those assessments.

CPVI will be performed by experienced operators who have prior experience with the NAVISTAR® THERMOCOOL® and/or EZ STEER® THERMOCOOL® NAV catheters (>50 AF ablation case per year). Before study initiation, operators will be trained on the use of the CF-guided ablation catheter and CARTO®3 VisiTag module for at least 5 patients. Investigators will set

personal operating reference ranges using experience gained from this training and the information of the prior clinical (human) studies and published literature. These patients will not be included in the study.

3.4 Subject Selection - Inclusion Criteria

Candidates for this study must meet ALL of the following criteria:

1. Age 18 years or older
2. Failure of at least one antiarrhythmic drug (AAD) for AF (class I or III, or AV nodal blocking agents such as beta blockers and calcium channel blockers) as evidenced by recurrent symptomatic AF, or intolerance to the AAD
3. Patients with paroxysmal AF eligible for catheter ablation
4. Patients with symptomatic PAF who have had at least one documented AF episode in the twelve (12) months prior to enrollment. Documentation may include but is not limited to electrocardiogram (ECG), Holter monitor (HM) or transtelephonic monitor (TTM)
5. Able and willing to comply with all pre-, post- and follow-up testing and requirements
6. Be able to sign IRB/EC-approved informed consent form

3.5 Subject Selection - Exclusion Criteria

Candidates for this study will be EXCLUDED from the study if ANY of the following conditions apply:

1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause
2. Previous surgical or catheter ablation for AF
3. Any PCI, cardiac surgery, or valvular cardiac surgical or percutaneous procedure (e.g., ventriculotomy, atriotomy, and valve repart or replacement and presence of a prosthetic valve) within the past 2 months.
4. Any carotid stenting or endarterectomy.
5. Coronary artery bypass graft (CABG) procedure within the last 180 days (6 months)
6. AF episodes lasting longer than 7 days or terminated via cardioversion
7. Documented left atrial thrombus on imaging
8. Uncontrolled heart Failure or New York Heart Association (NYHA) class III or IV
9. Myocardial Infarction within the previous 60 days (2 months)
10. Documented thromboembolic event (including TIA) within the past 12 months
11. Rheumatic heart disease
12. Awaiting cardiac transplantation or other cardiac surgery within the next 365 days (12 months)
13. Significant pulmonary disease, (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces chronic symptoms.
14. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study
15. Active illness or active systemic infection or sepsis
16. Diagnosed atrial myxoma

17. Unstable angina within the past 60 days (2 months)
18. History of blood clotting or bleeding abnormalities
19. Life expectancy less than 365 days (12 months)
20. Hypertrophic obstructive cardiomyopathy
21. Presence of implanted ICD
22. Contraindication to anticoagulation
23. Contraindication to isoproterenol
24. Presence of intramural thrombus, tumor or other abnormality that precludes catheter introduction or manipulation
25. Presence of a condition that precludes vascular access.
26. Women who are pregnant and/or breast feeding
27. Patients presenting contraindications for study catheter(s), as indicated in the respective Instructions For Use
28. Enrollment in an investigational study evaluating another device, biologic, or drug.

3.6 Subject Disposition

- **Enrolled Subjects:** patients who sign the informed consent.
- **Excluded Subjects:** subjects that are enrolled but never undergo insertion of the Study Catheter. Excluded subjects will not be evaluated in this study.
- **Discontinued Subjects:** subjects that have the investigational catheter inserted but are not treated with the investigational device (ie, no RF energy applied). Subjects will be categorized as "discontinued" if ablation was not possible due to non-investigational equipment failure or if their arrhythmia was determined at the time of electrophysiologic study to be a non-study arrhythmia (eg, atrial flutter).
- **Lost to Follow-up Subjects:** all subjects should be encouraged to return for protocol required office, clinic visit for evaluation during the study follow-up period. If a subject is unable to return for an office or clinic visit or unable to be contacted by telephone, 3 separate telephone calls should be made to obtain subject related safety information. All attempts should be documented in the source documents. If the subject does not respond to the 3 telephone calls, then the investigator must send a certified letter to the subject. If the subject does not respond to the letter, then the subject will be considered "lost to follow-up" for the current study visit. Subject contact must be attempted at each follow- up time point and if unable to contact the subject after 3 phone calls, the subject should once again be sent a certified letter. Only after failing to contact the subject at the final follow-up visit, the subject will be considered lost to follow-up and the study termination will be recorded in the individual case report form.
- **Withdrawn / Early Termination Subjects:** The investigator may remove a subject from the study for any of the following reasons: no longer meets eligibility criteria; withdrawal is in the subject's best interest; subject preference; concurrent illness; noncompliance; or any other situation the investigator deems a compromise to the integrity of the study. Subjects will be informed prior to study entry that they are free to withdraw from the study at any time and for any reason, without prejudice to his or her future medical care by the physician or the institution.

If a subject is removed from the study, the date and reason for withdrawal will be recorded on the appropriate case report form (CRF). If the subject is withdrawn due to an adverse event (AE) or serious adverse event (SAE), the Investigator must comply with all reporting requirements and must follow the subject until the AE/SAE has resolved or stabilized.

• **Completed Subjects:** enrolled subjects who have not expired or been discontinued, withdrawn or lost-to-follow-up from the study, prior to the final 1-year study visit.

4.0 Study Endpoints

4.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint for this study is freedom from documented symptomatic atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL) episodes through 12-month follow-up after the index ablation procedure (includes a three-month blanking period).

AF/AFL/AT qualifies as an arrhythmia recurrence after the first ablation if it lasts ⩾30 seconds and is documented by ECG, HM or TTM, etc.

The following will also be considered primary effectiveness failures and will be included in the effectiveness analysis cohorts:

- Acute procedural failure (ie, failure to confirm entrance block in all pulmonary veins with an isoproterenol intravenous challenge 0.5h post procedure or use of a non-study catheter to treat the study arrhythmia)
- A repeat ablation beyond the 90-day blanking period

Atrial tachyarrhythmia recurrence events will be recorded and included in study analysis after a 90-day blanking period; recurrence during the blanking will not be considered treatment failure; re-ablation will not be recommended during the blanking[12,53].

4.2 Secondary Endpoints

4.2.1 Acute Success Rate

Acute success is defined as confirmation of entrance block in all PVs with an isoproterenol intravenous challenge 0.5h post procedure.

The following test subjects will be considered as acute failures:

- Entrance block not confirmed for all PVs
- Subjects in whom a non-study catheter has been used for initial ablation of any AF targets

Acute failures will be considered primary effectiveness failures. Malfunction of a non-investigational catheter during the AF procedure will not be considered an acute failure.

4.2.2 CF and Force Time Integral (FTI) for index procedure by PV segments (from PV to the atrium, divided into 3, 6, 9 and 12 point position)(as shown in the figure below)

4.2.3 Number, percentage and sites of PV reconnection for the index procedure (from PV to the atrium, divided into 3, 6, 9 and 12 point position) (as shown in the figure below)

4.2.4 Total procedural, ablation (RF) time and fluoroscopy time

4.2.5 The incidence of AEs related with the procedure and study catheter

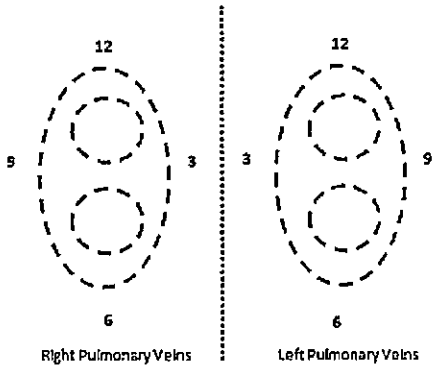

Figure 1: Right/left pulmonary veins was divided into 3, 6, 9 and 12 point position from PV to the atrium

5.0 Treatment Description

5.1 Patient Screening

A screening log, maintained at each study site, will be used to document all subjects reviewed for potential enrolment into the study. The screening log should be completed for any patient considered for study inclusion, regardless of whether the patient is selected or not, because this will allow better management of the study enrolment rate.

Patients who sign the patient Informed consent form will be considered enrolled in the study. A copy of the Patient Informed Consent template is provided. No patient should undergo any study-specific tests or exams that fall outside the standard of care without first signing the patient informed consent document for this study. An informed consent document must be obtained for a patient that is a potential study candidate prior to collection of any study related data.

5.2 Study Medications

The following medications are recommended for subjects undergoing the study catheter ablation for AF according to the 2012 CSPE Treatment Guideline FOR Atrial Fibrillation.[53]

Medication Prior to AF Ablation Procedure

- AAD should be discontinued at least five half-lives prior to the AF ablation procedure
- Standard anticoagulation therapy is recommended prior to the AF ablation procedure

Medication During AF Ablation Procedure

- Anticoagulation therapy is recommended during the AF ablation procedure
- Isoproterenol: An isoproterenol intravenous challenge is recommended 0.5h after the CPVI procedure to confirm the entrance block and exit block.

Medication Following AF Ablation Procedure

- Standard anticoagulation therapy is recommended post ablation procedure[12,53]

5.3 Pre-Procedure Assessments

Pre-procedure assessments should be performed prior to the index AF ablation procedure.

- To detect LA thrombi, e.g. routine TEE (Transesophageal Echocardiogram) on the day or the day before AF ablation
- ECG/ HM
- Baseline Medical history
- Arrhythmia history
- Baseline Cardiac Medications (including anticoagulation regime)

5.4 General AF Procedure Guidelines

The AF ablation procedures for this study should follow standard clinical practice guidelines[53].

- Diagnostic catheter placement
- Electrophysiology study (discretion of investigator)
- Transseptal puncture
- Cardioversion if subject is in AF (discretion of investigator)
- Introduction of the Study Catheter
- CARTO® 3 mapping of the targeted Left Atrium (LA)
- Ablation of targets
- An isoproterenol intravenous challenge is required 0.5h after the CPVI procedure to confirm the entrance block and exit block

In the event of spontaneous or induced AF and/or atrial flutter, the placement of additional RF lesions outside of the PV ostia is at the discretion of the investigator and includes the following:

- Ablation at sites exhibiting complex fractionated atrial electrograms (CFAE)
- Linear lesions （If linear lesions are placed, it is recommended that complete conduction block across the ablation line be demonstrated）

•Ablation for any non-PV foci in the LA and/or RA

Any sheath except Agilis can be used in conjunction with ST catheter during the procedure. Cardioversion will be allowed if deemed clinically necessary by the investigator.

5.5 Follow-up Visit Assessments

All subjects will be followed through one year after the index ablation procedure. Blanking period will span 90 days.

After the index AF ablation procedure, subject follow-up visits are required at 3 months (Day 90: 76-104 days), 6 months (Day 180; 166-210 days), 9 months (Day 270; 240-300 days), and 12 months (Day 360; 330-420 days). Follow-up visit schedule will not reset if subject undergoes a repeat AF ablation procedure with the study catheter.

At each visit, the following assessments should be performed:

- AF/AT/AFL recurrence and repeat ablation
- ECG, HM and TTM
- Current AAD (including anticoagulation regime)
- Adverse events

If a subject returns for an arrhythmia related visit outside of the protocol-defined visit schedule provided, the visit will be considered "unscheduled" (UNS). For all arrhythmia related unscheduled visits, an unscheduled visit CRF must be completed. If the unscheduled visit is for a repeat ablation procedure, the protocol follow-up schedule will be based on the index procedure.

5.6 TTM

Transtelephonic monitors (TTM) will be provided to each subject at the 3-month follow-up visit (post-blanking) for scheduled transmissions of heart rhythm status.

The TTM transmission schedule:

- Transmission will be weekly during the first 8 weeks after the blanking period (starting day 91).
- After the first 8 weeks, asymptomatic transmissions will be transmitted monthly until the end of the 12-month follow-up visit. All symptomatic arrhythmia episodes should be recorded and transmitted at the time the event occurs.

5.7 Management of Arrhythmia Recurrence During Follow-up

Repeat AF ablations(s) may be performed at the discretion of the physician in accordance with current AF management guidelines.[11,13,32-34,53] The follow-up schedule will remain based on the initial AF ablation procedure performed with the Study Catheter. All re-ablation procedures must be fully documented in CRF.

5.8 Data Collection flow chart

	Baseline/Pre-Ablation	Ablation	Pre-Discharge	3M [Days 76-104]	6M [Days 166-210]	9M [Days 240-300]	12M [Days 330-420]	UNS[3] (as needed)
Clinic visit	X			X	X	X	X	X
Informed Consent	X							
Demographics	X							
Medical history	X							
Ablation parameter values		X						
AF status	X		X	X	X	X	X	X
Past and current Cardiac medication	X		X	X	X	X	X	X
Current anticoagulation regime	X		X	X	X	X	X	X
ECG	X		X	X	X	X	X	X
24h Holter	X			X	X	X	X	X
Examination to detect LA thrombi[1]	X							
TTM [2]				X	X	X	X	X
AF/AT/AFL recurrence				X	X	X	X	X
Repeat ablation				X	X	X	X	X
Adverse events		X	X	X	X	X	X	X

1. To detect LA thrombi, e.g. routine TEE on the day or the day before AF ablation.
2. TTM transmission will be weekly during the first 8 weeks after the blanking period; After the first 8 weeks, asymptomatic transmissions will be transmitted monthly until the end of the 12-month follow-up visit. All symptomatic arrhythmia episodes should be recorded and transmitted at the time the event occurs.
3. If a subject returns for an arrhythmia related visit outside of the protocol-defined visit schedule provided, the visit will be considered "unscheduled" (UNS).

6.0 Adverse Events

6.1 Adverse Event Reporting

An adverse event (AE) is any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject during the course of the registry, whether or not it is related to the device or procedure. Physical findings (including

vital signs) observed at follow-up, or pre-existing physical findings that worsen compared to baseline, are adverse events if the investigator determines they are clinically significant.

6.2 Classification

6.2.1 Serious AEs

A serious adverse event is any event that meets one or more of the following criteria:

- Led to a death Led to a death
- Led to a serious deterioration in the health of the subject that
    a. Resulted in life-threatening illness or injury,
    b. Resulted in permanent impairment of a body structure or a body function,
    c. Required hospitalization or prolongation of existing hospitalization
    d. Resulted in intervention such as medication or cardioversion to prevent permanent impairment of a body function or damage to a body structure, except for the treatment of a preexisting arrhythmia.
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

6.2.2 Non-Serious AEs

A non-serious adverse event is any event that results in minimal transient impairment of a body function or damage to a body structure, or which does not require any intervention other than those listed under the definition of "serious adverse event".

6.2.3 Anticipated AEs

An anticipated adverse event is an event that has been reported in previous studies of radiofrequency ablation and can be decided by the investigators if it is related to the study device or procedure in this study.

The event occurs within the first week (≤7 days) following an AF ablation procedure with the study catheter and is one of the following: atrial perforation/ cardia tamponade; myocardial infarction; perricarditis need to be intervented; embolism event; heart block; atrio-esophageal fistula; injury of phrenic nerve; injury of esophageal peripheral vagus nerve; acute coronary artery occlusion; vascular access complication; death,etc.

The event occurs within the first week (>7 days) following an AF ablation procedure with the study catheter and is one of the following: arrhythmias, embolism event, death,etc.

6.2.4 Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse event is a serious event not previously identified in nature, severity or degree of incidence, or any other serious problem associated with the device that relates to the rights, safety or welfare of subjects.

6.3 Reporting Requirements

The investigator must submit the completed Adverse Event Form to sponsor (or designee), any Unanticipated Adverse Device Effects (UADE) and SAEs occurring during the study, within 24 hours after becoming aware or being notified of the event, and provides additional information, if requested by JJMS.

The investigator is required to notify Local/Central EC of all SAEs and UADEs that occurred at his/her site in accordance with the Ethics Committee provisions.

The sponsor will report to all participating clinical investigators all deaths and UADEs within 5 working days after the sponsor first receives notice of the effect and/or event. The sponsor will submit every year (unless otherwise indicated by the Ethics Committee or recommended by the local regulations to all participating clinical investigators an update of all study devices related, site reported and adjudicated SAEs. A letter summarizing the study status, enrollment figures, any safety concerns will accompany the updates.

All AEs recorded must be followed until resolution or until a stable clinical endpoint is reached. If the patient is treated for an event outside the treating hospital, the site should try to obtain copies of any documentation containing pertinent information related to that specific event.

6.4 Intensity or Severity

The intensity or severity of each AE must be assessed according to the following classifications:

• Mild	Any event that results in minimal transient impairment of a body function or damage to a body structure, and/or does not require intervention other than monitoring.
• Moderate	Any event which results in moderate transient impairment of a body function or damage to a body structure, or which requires intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure.
• Severe	Any event which is life threatening, which results in permanent impairment of a body function or damage to a body structure, or which requires significant intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure.

6.5 Outcome

The outcome of each AE must be assessed according to the following classifications:

Resolved	Subject fully recovered with no observable residual effects.
Improved	Subject's condition improved, but residual effects remain.

Unchanged	AE is ongoing.
Worsened	Subject's overall condition worsened.
Death	Subject died as a result of the AE (whether or not the AE is related to the device or procedure).

6.6 Causality

The causality of each AE must be assessed according to the following classifications:

Device-related	The device directly caused or contributed to the AE.
Possibly Device-related	The device may have caused or contributed to the AE.
Procedure-related	The event is directly associated by timing and/or pathophysiology with the standard electrophysiology or ablation procedure described in this protocol.
Possibly Procedure-related	The AE may be associated by timing and/or pathophysiology with the standard electrophysiology procedure described in this protocol.
Not Related	The AE is not associated with either the device or the procedure described in this protocol.

6.7 Documentation

All AEs must be documented on the appropriate CRF. All AEs must be monitored until they are adequately resolved or explained. Each AE must be reported regardless of classification and seriousness, intensity, outcome or causality.

Documentation may be requested by the Sponsor, including but not limited to, a written subject narrative detailing the clinical course of the AE, a copy of any correspondence with the local Ethics Committee (EC), hospital records, and an autopsy report, if available.

7.0 PRODUCT COMPLAINTS

The post-market product complaints in this study will be submitted according to Chinese regulations. There are no specified products being investigated for this study; hence product complaint information will not be collected on eCRFs as part of this study.

Product complaints on JJMS devices must be reported to the China Complaint Handling Unit (CHU) as soon as possible (no later than 24 hours after becoming aware of the event). Reporting should follow the established local process at the site. The China CHU will ensure follow-up of the product complaint and initial reporting to the device manufacturer. The local JJMS representative must fax the Product Complaint Form to the China CHU at the following: JJMC-productcomplaint-Cordis@its.jnj.com. Subsequently, the local JJMS representative will contact the respective physician, assisting in recording the necessary details. The device should be retained, and the China CHU will assist in the collection and return of the device to

the JJMS device analysis site. It is the intent of JJMS to perform a complete evaluation of the device.

8.0 Statistical Analysis

8.1 Clinical Study Objective

The objective of this study is to assess the effectiveness and safety in the treatment for drug refractory symptomatic PAF subjects with the THERMOCOOL® SMARTTOUCH™ catheter undergoing CPVI.

8.2 Sample Size and Power Calculation

Assuming the true rate for freedom from documented symptomatic AF, AT, or AFL episodes through 12-months follow-up is about 65% with CF-guided approach and a historic control performance goal of 50%, [12] a sample size of 150 is needed in order to have 95% power to have the lower bound of the two-sided 95% confidence interval of this recurrence free rate above the historic control performance goal. This sample size is computed using nQuery Advisor® version 7.0. Considering 20% dropout rate, a sample size of 188 is needed. This study will enroll approximately 200 subjects(no less than 188).

8.3 Analysis Population

Intent-to-treat (ITT) Population: Enrolled subjects who meet the inclusion/exclusion criteria. ITT Population will be used for baseline summary and provide primary analysis for efficacy endpoints.
Safety (SS) Population: Enrolled subjects who have undergone insertion of the study catheter. Safety Population will be used for the summaries for safety endpoints.
Per-protocol (PP) Population: Subjects in the ITT Population who have undergone insertion of the study catheter and AF ablation procedure, and do not have other major protocol violations PP Population will be used to provide supportive analysis for efficacy endpoints.

8.4 Statistical Analysis of Study Endpoints

8.4.1 General Analytic Methods

All statistical procedures will be completed using SAS version 9.2 or later version. Analysis for this study will mostly be descriptive. Summary statistics will be provided. For continuous variables, this will include the number of observations, mean, median, standard deviation, minimum, and maximum. For categorical variables, this will include frequency counts and percentages.

Hypothesis testing will be carried out at the two-sided α=0.05 level unless otherwise specified; 2-sided 95% confidence intervals will be presented, where specified.

Further details regarding the analysis, data handling rules and data displays will be described in the Statistical Analysis Plan (SAP). SAP will be signed off before the database lock.

8.4.2 Primary Endpoint

The primary effectiveness endpoint for this study will be freedom from documented symptomatic AF, AT, or AFL episodes through 12-months follow-up after the index ablation

procedure (includes a three month blanking period). The number of subjects who achieved this endpoint and its percentage will be presented. A two-sided binomial exact 95% confidence interval will be computed. Superiority against historic control performance goal will be claimed if the lower bound of this confidence interval is above 50%.

A Kaplan-Meier analysis will be performed for the time to the first documented symptomatic AF, AT, or AFL episodes. The first quartile, median, and third quartile for the time to first AF, AT, or AFL episode through 12-months follow-up period will be presented. The 95% confidence intervals for the first quartile, median, and third quartile will be computed.

Baseline covariates and procedure parameters that affect the occurrence of AF, AT, or AFL episodes through 12-months follow-up period will be explored using logistic regression models.

8.4.3 Secondary Endpoints

For acute success rate, the number of subjects who achieved this endpoint and its percentage will be presented. A two-sided binomial exact 95% confidence interval will be computed.

For CF and Force Time Integral for index procedure by PV segments, descriptive summary statistics and 95% two-sided asymptotic confidence intervals will be presented.

For number of PV reconnection after the index procedure, descriptive summary statistics and 95% two-sided asymptotic confidence intervals will be presented. Percentage of PV reconnection after the index procedure will be computed for each subject. And then the descriptive summary statistics and 95% two-sided asymptotic confidence intervals will be used to summarize the percentage of PV reconnection across subjects. Frequency counts and percentages will be used to summarize the sites of PV reconnection after the index procedure.

For total procedural, ablation time and fluoroscopy time, descriptive summary statistics and 95% two-sided asymptotic confidence intervals will be presented.

Correlation between the secondary efficacy endpoints and the primary efficacy endpoint will be explored.

Adverse events observed during the study will be coded by Medical Dictionary for Regulatory Activities Medications (MedDRA). Adverse events will be summarized by System Organ Class (SOC) and Preferred Term (PT) using counts and percentages. Additional AE summaries by SOC, PT, and maximum severity, as well as AE summaries by SOC, PT, and relationship to study procedure will be provided. Serious AEs will also be summarized by SOC and PT.

9.0 Administrative Responsibilities

9.1 Independent Ethics Committee (IEC) Information

The protocol and amendments, informed consent form, adverting materials and other necessary study documents must be submitted to the appropriate EC for approval or archival. Approval from the EC must be obtained prior to starting any study-related procedure.

The investigator will promptly report to the EC all changes in research activity and all unanticipated problems involving risks to subjects or others and will not make any changes in the research without EC approval, except when necessary to eliminate immediate hazards to human subjects. Those amendments involving significant risk or change require EC approval, and written documentation of this approval must be submitted to JJMS before implementation, except in an emergency situation.

9.2 Patient Informed Consent

Informed consent is mandatory and the informed consent form signed and dated by both investigator and subject must be obtained from all subjects prior to CRF entering in this study. Any modifications to the Patient Informed Consent Form must be approved by JJMS and the IEC . The Informed Consent Form approved by IEC along with the consent forms signed by every subject must be maintained by investigator in a designated clinical trial master file. A signed copy of the consent form must be given to each subject.

It is the investigator's responsibility to ensure that the Informed Consent process is performed in accordance with GCP.

9.3 Confidentiality

All information and data sent to JJMS and the CRO of this trial concerning subjects or their participation in this trial will be considered confidential. Only authorized JJMS personnel, CRO of this study or other government authorities acting in their official capacities will have access to these confidential files. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the subject. Data will be analyzed at the CRO or authorized agency by JJMS. All subject information will be kept confidential. The database will be kept under password and lock protection.

9.4 Quality Control and Quality Assurance

9.4.1 Data Quality Assurance

Steps taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel prior to the study, and periodic monitoring visits by JJMS (or designee). Data in the electronic Case Report Forms (eCRF) will be reviewed for accuracy and completeness and compared with the source documents during on-site monitoring visits and any discrepancies will be resolved with the investigator or designee, as appropriate.

9.4.2 Source Data (SD)

It is the obligation of each investigator (or designee) to assure that the medical files and all other possible files are appropriately completed. The patient's file for each enrolled subject should clearly reflect the status of the patient.

The patient's file also should clearly show that the individual's data are used as a registry participant by entering the following details: study name, protocol number, date of enrollment, informed consent obtained before the enrollment. All data populated on eCRF will be regarded as source documents directly.

Each follow-up visit needs to be reported in the SD and should at least contain: all AE, concomitant medications, primary key points and general status of the subject.

9.4.3 Monitoring

JJMS will initiate the study after an on-site visit completed and all required documents have been received. JJMS (or designee) will continue to perform on-site monitoring visits as defined in the monitoring plan. Monitoring is performed to verify that the rights and well being of the subjects are protected, the study is conducted according to Good Clinical Practices (GCP) and to pertinent Chinese regulations, the protocol is followed, and the recorded data are accurately represented according to the source documentation.

At the monitoring visits the monitor will compare the data reported on the eCRFs with the source documents. At a minimum, source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events and concomitant medications, and device procedure information. Specific items required as source documents will be reviewed with the investigator prior to the study. Findings from this review of eCRF and source documents will be discussed with the investigator. The monitor will record the dates of the visits on a Monitoring Visit Log kept at the site. JJMS expects that during monitoring visits, the study coordinator and/or investigator will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents.

9.4.4 Protocol Modifications

All protocol amendments must be signed and dated by the investigator. The Institutional Ethics Committee (IEC) must approve substantial amendments prior to the implementation. The EC must be notified of non-substantial amendments.

9.4.5 On-Site Audits

This study may be audited by sponsor or regulatory authority inspectors. If such an audit occurs, the investigator must agree to allow access to required subject records. By signing this protocol, the investigator grants permission to personnel from the

Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation.

9.5 Records and Reports

9.5.1 Records

Records to be maintained by the investigator include:

- Signed Confidentiality agreement.
- Signed clinical trial agreement
- Clinical trial investigational plan and all amendments
- Institutional Ethics Committee (IEC) approval letter, including approved informed consent document
- Institutional Ethics Committee (IEC) membership list
- Screening log
- Correspondence relating to the trial
- CVs for all investigator(s), research coordinator(s), and/or research staff
- Medical license for PI
- Site personnel delegation signature list
- Site personnel training record
- Clinical monitor sign-in log
- Subject enrollment log
- Subject identification log
- Lab certification and lab test normal ranges
- EC notification/ acknowledgement
- Reports (includes annual reports, final reports from investigator and Sponsor)

The following records must be maintained for each subject enrolled in the trial:

- Signed Patient Informed Consent Form
- All source documentation used to complete eCRFs
- Supporting documentation of any complications and/or death.

The investigator must retain sources of procedure reports, procedure nursing notes and the results of any interventional procedures that occur during a subject's study enrollment. All source documents should be signed and dated by the investigator. JJMS reserves the right to secure data clarification and additional medical documentation on subjects enrolled in this trial.

9.5.2 Reports

Investigators are required to prepare and submit to JJMS complete, accurate and timely reports on this investigation, when necessary.

Records and reports will remain on file for a minimum of five (5) years after the completion/termination of the investigational trial. They may be discarded upon notification by JJMS. To avoid error, the principal investigator should contact JJMS before the destruction of any records and reports pertaining to the trial to ensure they no longer need to be retained. In addition, JJMS should be contacted if the principal investigator plans to leave the investigational site so that arrangements can be made for transfer of records and management of any active study subjects.

Responsibilities for Preparing and Submitting Reports

Type of Report	Prepared and Submitted by Investigator For	Time of Notification / Completion
eCRF	JJMS	Within 14 days
Subject death (peri-procedural)	JJMS, Institutional Ethics Committee	Within 24 hours of knowledge of event
Unanticipated AEs	JJMS, Institutional Ethics Committee	Within 24 hours of knowledge of event
Subject withdrawal	JJMS	Within 5 working days
Withdrawal of Investigational Review Board approval	JJMS	Within 5 working days
Annual progress report	JJMS, Institutional Ethics Committee	Submitted annually within 90 days of the IEC annual review date
Informed consent not obtained from subject	JJMS, Institutional Ethics Committee	Within 5 working days

9.6 Investigator's Final Report

Upon completion or termination of the study, the principal investigator must submit a final written report to JJMS and the Institutional Ethics Committee (IEC). The report should be submitted within 3 months of completion or termination of the trial.

The investigator's final report will include:

- Introduction: A brief description of the rationale and objectives of the trial.
- Methods: A description of the methods employed and all protocol deviations.

- Trial Population: A statement of the number of subjects evaluated; of the
- Number of dropouts and reasons for them; and description of the initial nature and severity of medical conditions for which the subjects were evaluated.
- Results and Discussions: A clinical assessment of the investigational device, on the medical condition of the subjects, and a description of complications reported with an indication of their relationship to the investigational treatment.
- Conclusion: A summary statement of the principal investigator's opinion of the investigational device in the subjects enrolled at his/her investigational site.

9.7 Deviations from Protocol

The investigator will not deviate from the protocol without the prior written approval of JJMS except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the subject's risk or affect the validity of the trial. In medical emergencies, prior approval for protocol deviations will not be required, but the JJMS Clinical Research Personnel must be notified within 5 days of the incident.

10.0 Study Data Reporting and Processing

All eCRFs should be thoroughly filled-out within 14 days of receiving the source documents.

10.1 Study Data Collection

The final set of eCRFs is designed to accommodate the specific features of the study design. Modification of eCRFs will only be made if deemed necessary by JJMS or investigators.

10.2 Site Data Monitoring and Quality Control

Primary data collection based on source-documented reviews will be performed by study coordinators or research designee at the clinical site. eCRFs will be completed timely in an expedited fashion. The clinical site will be audited periodically by Sponsor personnel or designee for protocol adherence, accuracy of eCRFs, and compliance to applicable regulations. Any evident pattern of non-compliance with respect to these standards will be cause for the site to be put on probation. If corrective actions are not subsequently undertaken, the clinical site will be asked to withdraw.

10.3 Data Processing and Quality Control

CRO, was authorized agency by JJMS, will employ a database on a central server, networked to data entry and data analytical workstations. Periodic analysis of each data field (across cases) will be performed in order to examine the expected distributions of data, and to identify outliers for possible data mistakes.

The tables and data entry screens will be created according to CRO standard. Data entry and verification will be carried out and Coding of the study will be performed by the CRO. More detailed information, please see to Data Management Plan.

10.3.1 Data Verification

All eCRFs will be subjected to initial inspection for omitted data, gross data in consistencies, and timeliness of reporting. Any deficiencies will be resolved during the monitoring visit.

10.3.2 Data Update

The cycle of data edits will be ongoing until all the data are clean. The Sponsor or designee will monitor the clinical site for source documentation verification. If further data entry or source documentation errors are discovered during the monitoring visit.

10.3.3 Final Data Analyses

All exported datasets for analyses will undergo a final data verification procedure. Once all data are cleaned and locked, the data will undergo final analyses.

More detailed information, please see to Statistical Analysis Plan.

10.4 Training

The training of appropriate clinical site personnel will be the responsibility of the Sponsor. To insure uniform data collection and protocol compliance, Sponsor personnel will present a formal educational session to study site personnel that will review the Investigational Plan, techniques for the identification of eligible subjects, instructions on in-hospital data collection, schedules with the study site coordinators and/or investigators, and regulatory requirements. Detailed telephone, fax and email feedback regarding completion of forms will be provided by the Sponsor, and through the regular site monitoring.

11.0 Study Management

11.1 Investigator Selection

Principal Investigator

The principal investigator's responsibilities include:

- Ensuring that all investigators comply with the ablation treatments described in the protocol.
- Advising the Sponsor of any unforeseen medical issues identified during the clinical study.
- Supporting the Sponsor's efforts in conducting periodic investigator meetings and Adverse Event relevant meetings.

11.2 Investigator Responsibilities

Investigators at clinical site will have the following responsibilities:

- Providing the Sponsor with:
  - Signed, dated Study Agreement,
  - Signed, dated Financial Disclosure form,
  - Curriculum vitae for each Investigator which were authorized.
- Maintaining an accurate and current Study Personnel Log which identifies all those individuals authorized to perform work for the investigation at each site
- Undergoing the appropriate training on the device and the study protocol prior to enrolling and treating subjects

Obtaining informed consent from patients

- Performing the ablation procedure
- Compliance with the clinical protocol
- Notifying the Sponsor/IRB of adverse events and deaths in the timeframes defined in this protocol
- Compliance with IRB and Sponsor annual report requirements
- Maintaining accurate and current logs for the study such as: Screening Log and Subject Identification log.
- Accurate and timely completion of eCRFs.
- Reviewing and signing designated eCRFs
- Maintaining relevant source documentation to support data on the CRFs.

• Efforts to maintain contact with all treated subjects who fail to comply with the follow-up requirements. Before a subject may be classified as 'lost to follow-up',the Investigator or authorized personnel should document at least four attempts to contact the subject: three (3) by documented phone calls and one (1) written attempt sent by registered mail. If the subject is contacted but does not wish to complete the required follow-up, investigator will be asked to provide a written statement confirming that he/she is no longer willing to participate in the study.

• Prepare a final report and periodic IRB updates as required.

11.3 Sponsor Responsibilities

• Redacted

11.4 The CRO Responsibilities

• Redacted

11.5 Initiation of the Investigation

The investigational site will undergo an evaluation to ensure that the site has the appropriate facilities and personnel to conduct the study in compliance with the Investigational Plan (protocol).

The participating site will be provided with the appropriate training prior to commencement of the study. To insure uniform data collection and protocol compliance, the Sponsor will present a formal educational session to study site personnel that will include review of the Clinical Study Protocol, techniques for the identification of eligible subjects, instructions on in-hospital data collection, follow-up schedules with the study site coordinators, and regulatory requirements.

11.6 Monitoring the Investigation

The study site will undergo periodic monitoring of the investigation, which involves a monitoring visit from a Sponsor representative, qualified to perform such monitoring visit. Each monitoring visit will encompass some or all of the following items:

- Verify that all study records are being kept current and accurate.
- Verify that all subjects have a current, signed, dated Informed Patient Consent Form
- Verify that required study documentation was collected such as investigator CVs
- Verify that study correspondence is being maintained
- Monitor the eCRFs with the source documents
- Identify and resolve any issues or problems with the study

11.7 Termination of the Investigation

At the termination of the investigation, the study site will undergo a monitoring visit to conclude any outstanding issues, resolve all outstanding eCRFs, discuss the required final report from the Principal Investigator, and discuss any other items relevant to the conclusion of the study. This termination visit will be documented by a written report.

Any incidence of unanticipated serious adverse device effect may result in the early termination or suspension of the clinical study. All enrolled subjects will continue to be followed per the study protocol requirements.

11.8 Electronic Case Report Forms (eCRF)

eCRFs have been developed to capture the information outlined in this Investigational Plan. Data on these eCRFs will be monitored and corrected in timely fashion. All changes made to the data will be tracked in the electronice audit trail, recording the current value, previous values, reason for change, date timestamp of data entry/change, and the name of the person who changed the data.

The Principal investigator will sign and date eCRF set as verification that they have been reviewed and the data are correct. Data from these eCRFs will be used to provide analysis of this study.

11.9 Source Documentation

Data entered on to the eCRFs will be taken from source documentation, such as hospital procedure reports, admission and discharge summaries, and other hospital or physician office/clinic documents. If no standard hospital or office document exists to capture some of the information that may be unique to this study, a worksheet may be developed to record this information, which shall be signed by the investigator(s) at the site, and which will serve as the source document for those data parameters. These source documents will serve as the basis for monitoring the eCRFs.

11.10 Subject Confidentiality/Record

For the duration of this investigation, all representatives of the Sponsor will comply with all regulations in China regarding contact with subjects, their medical record information, copying of information, protection of the subject identities, and all other aspects of regulations. Authorization for access to protected health information by Sponsor personnel which was authorized should be obtained as part of subject informed consent.

11.11 Data Management

The Sponsor will collaborate with its CRO provider to perform all data management activities. These activities include the development of a master database and utilization of validated database software into which all study data will be entered.

12.0 Regulatory / Ethical Considerations

12.1 Role of JJMS

As the study Sponsor of this clinical study, JJMS has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the State Food and Drug Administration of China.

12.2 Maintaining Records

JJMS will maintain copies of correspondence, data, adverse device effects and other records related to the clinical trial.

JJMS will maintain records related to the signed Study Agreements.

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