Protocol No.: EP034

Clinical Trial Protocol for Pre-market Registration of Biotronik Qubic Stim Cardiac Stimulator

Name of Investigational Medical Device: Cardiac Stimulator

Component and Model of Investigational Medical Device

Component name	Model
Stimulation unit	Qubic Stim – EP Heart Stimulator
Control unit	Qubic Stim – Control Unit
Patient cable	PK-128

Management Category of Investigational Medical Device:

Class III medical device requiring the clinical trial approval: Yes□ No■

Predicate products in China: Yes■ No□

Protocol No. and Date: V2.0 2020-4-28

Clinical Trial Institution: China-Japan Friendship Hospital

Investigator: Yifeng Zhou

Sponsor: BIOTRONIK SE & Co.KG

Agent: BIOTRONIK (Beijing) Medical Device Limited

Notes:

1. For multi-center clinical trials, only the leading unit is listed as the clinical trial institution on the cover while other institutions are listed in the Protocol.
2. For multi-center clinical trials, only the coordinating investigator is listed as the investigator on the cover.
3. BIOTRONIK (Beijing) Medical Device Limited is hereinafter referred to as BIOTRONIK.

Content

1 Protocol Summary

Name of study	Clinical Trial for Pre-market Registration of Biotronik Qubic Stim Cardiac Stimulator
Purpose of study	To prove the clinical effectiveness and safety of Qubic Stim Cardiac Stimulator in Chinese population.
Study design	The trial is a multicenter, prospective and single-arm study. 106 appropriate subjects were selected from 3 study sites in China in accordance with the inclusion and exclusion criteria. The subjects consent to participate in the trial and sign the informed consent. The subjects who meet the inclusion and exclusion criteria will receive the intracardiac electrophysiological examination, during which the subjects will be subject to diagnostic electrical stimulation by the Qubic Stim Cardiac Stimulator. The subjects will also receive the clinical follow-up visit after cardiac electrical stimulation until they are discharged from the hospital. The clinical effectiveness and safety of Qubic Stim Cardiac Stimulator in Chinese population were proved by observing the data collected in this study.
Sample size	106 cases
Study site	3 study sites in China
Investigational device	Qubic Stim Cardiac Stimulator
Study population	Patients with indications for intracardiac electrophysiological examination
Study period	Enrollment time of the first batch of subjects: October 2020 Expected inclusion period: 3 months End of follow-up: Feburary 2021
Inclusion criteria	1. Age ≥ 18 years 2. Subjects who are willing to participate and sign the informed consent form，and are able to finish the follow-up at the study site. 3. Subjects with an indication of the intracardiac electrophysiological examination(fit one of the following): ➢ Paroxysmal supraventricular tachycardia: atrioventricular reentrant tachycardia or atrioventricular node reentrant tachycardia or atrioventricular tachycardia ➢ Ventricular arrhythmia: Premature ventricular contraction or ventricular tachycardia. ➢ Atrial fibrillation ➢ Atrial flutter
Exclusion criteria	1. Previous cases of unsuccessful radiofrequency ablation or recurrence 2. Pregnant and/or lactating women 3. Acute or severe systemic infection was present within 7 days prior to the intracardiac electrophysiological examination 4. Liver and kidney functions were obviously abnormal within 7 days prior to the

	intracardiac electrophysiological examination 5. Obvious bleeding tendency or blood system disease 6. Cancer and terminal disease 7. Combined with severe organic cardiovascular disease 8. Cerebral apoplexy and other cerebrovascular diseases within the past 3 months 9. Thromboembolic disease 10. Subjects who are participating in other interventional clinical trials
Primary clinical observation indexes	The success rate of the Qubic Stim cardiac stimulator to send diagnostic electrical stimulation to the heart. The success standard refers to that all the main functions of the cardiac stimulator meet the success standards, including: 1. Programmed extrastimulation (PES) Expected clinical effect: PES can effectively pace the heart at a set rate of stimulation. 2. High Rate (Burst) Expected clinical effect: when the tachycardia is induced or terminated by high rate stimulation, this device can effectively pace the heart according to the set stimulating frequency. 3. Measurement of Sinus node recovery time (SNRT) Expected clinical effect: SNRT can be measured. This trial will conduct cardiac electrical stimulation by the main functions of the cardiac stimulator above. Only when the above three functions all reach the standards in particular subjects, it is judged as stimulation success. The main evaluation index corresponds to the proportion of the patients who achieve the success standards.
Secondary clinical observation index	Serious device adverse events caused by cardiac stimulator
Follow-up arrangement	1. Baseline evaluation: when the subjects were enrolled. 2. Electrical cardiac stimulation: the period during which the subjects receive the intracardiac electrophysiological examination. 3. Pre-discharge assessment
Sponsor	BIOTRONIK SE & Co.KG

2 Sponsor Information

Name of sponsor	BIOTRONIK SE & Co.KG
Address of sponsor	Woermannkehre 1 12359 Berlin, Germany
Contact information of sponsor	Mathias Freudigmann +49 (0) 30 68905 1248 mathias.freudigmann@biotronik.com
Relevant qualification documents of sponsor	TUV certification of production enterprise quality system
Name of agent	BIOTRONIK (Beijing) Medical Device Limited
Address of agent	Room 1122, 1123AB and 1125, Interchina Commercial Building, No. 33, Dengshikou Street, Dongcheng District, Beijing
Contact information of agent	Lan Chen 13811648209
Relevant qualification of agent	Unified social credit code certificate of enterprise and business license

3 List of All Clinical Trial Institutions and Investigators in Multicenter Clinical Trial

Code of clinical trial institutions	Name of clinical trial institutions	Investigator	Title	Contact information
01	China-Japan Friendship Hospital	Yifeng Zhou	Chief Physician	13811750398
02	TEDA International Cardiovascular Hospital	Jian Zhang	Chief Physician	13920642460
03	The First Affiliated Hospital of Nanchang University	Jingtian Peng	Chief Physician	13007227250

4 Purpose and Content of Clinical Trial

4.1 Purpose

It is intended to prove the clinical effectiveness and safety of Qubic Stim Heart Stimulator in Chinese population.

4.2 Content

This is a multicenter, prospective and single-arm study. 106 appropriate subjects were selected from 3 study sites in China in accordance with the inclusion and exclusion criteria. The subjects who meet the inclusion and exclusion criteria will receive the intracardiac electrophysiological examination after signing the informed consent, during which the subjects will be subject to diagnostic electrical stimulation by the Qubic Stim Cardiac Stimulator. The subjects will also receive the clinical follow-up after cardiac electrical stimulation until they are discharged from the hospital. The clinical effectiveness and safety of Qubic Stim Cardiac Stimulator in Chinese population were further demonstrated and proved by observing the data collected in this study.

5 Background Information of Clinical Trial

Intracardiac electrophysiological (EP) examination is widely used to evaluate cardiac conduction disturbance and arrhythmias. The risks associated with this procedure, particularly the use of an extracorporeal programmed stimulator, are generally acceptable and the patient benefits are considered to outweigh the risks. Diagnostic EP examination is usually combined with the treatment of a diagnosed heart disease, such as catheter ablation of arrhythmia. In addition, the results of EP examination may indicate the need for specific drugs or implantation of a pacemaker or cardioverter defibrillator for treatment.

As a manufacturer of implantable cardiac stimulator and ablation catheter, BIOTRONIK SE & Co.KG has marketed more than 1,300 extracorporeal programmed stimulators for EP examination since 1982, including UHS 20 device and the updated UHS 3000. Both of the devices are used for clinical EP examination. Qubic Stim device is an iterative product of UHS 3000 Universal Cardiac Stimulator. The two devices have similar operation function, intended use and indications. Other medical device manufacturers active in the cardiac EP diagnosis and treatment market also provide a series of extracorporeal programmed stimulators, which are used in the same clinical environment as Qubic Stim device.

The clinical evaluation of Qubic Stim Stimulator (software release version UHS_SE1.9; UHS_BE1.8) and PK-128 patient-end cable is provided by BIOTRONIK SE & Co.KG in accordance with the requirements of MEDDEV 2.7.1 Guidelines for Clinical Evaluation of Medical Devices. No uncertain risk emerged in the risk management process of Qubic Stim device and PK-128 patient-end cable based on published literature in the public domain, manufacturer's clinical

experience and results of device availability test. The safety and performance of the device are well validated by clinical evaluation. This medical device meets the basic requirements of European Union (EU) Medical Device Directive. In Europe no further clinical data is needed to prove the safety of Qubic Stim device and PK-128 patient-end cable. This device is clinically equivalent to the most advanced commercially available competitor device, and Qubic Stim performance is suitable for the most advanced EP diagnostic stimulation.

6 Product Characteristics, Structure Composition, Operating Principle, Action Mechanism of Product and Trial Stretch

6.1 Product characteristics

Qubic Sim system is an active and non-invasive medical device runs on software, which is mainly used in combination with other diagnostic medical devices. The Qubic Stim control units and stimulation units are provided in a non-sterile manner and are not suitable for sterilization.

PK-128 patient-end cable is sterile and can be re-sterilized in sterile area. However, the patient-end cable is connected to other equipment (see Figure 1) in current clinical practice, in which case the patient-end cable does not enter the sterile area and does not need sterilization.

The Qubic Stim device is used for invasive cardiac surgery based on its intended application.

6.2 Product structure, operating principle and action mechanism

6.2.1 System structure and settings

Qubic Stim system includes control unit and stimulation unit, which are connected with each other via Ethernet cable (VK-118). Although software release version UHS_SE1.9; UHS_BE1.8 supports the single control unit, stimulation unit hardware is still used to connect two separate control units for future development. The stimulation unit is connected to other devices through PK-128 patient-end cable. An overview of typical device connection including the Qubic Stim system and PK-128 patient cable is shown in Figure 1. Details about PK-128 patient-end cable are shown in Figure 2.

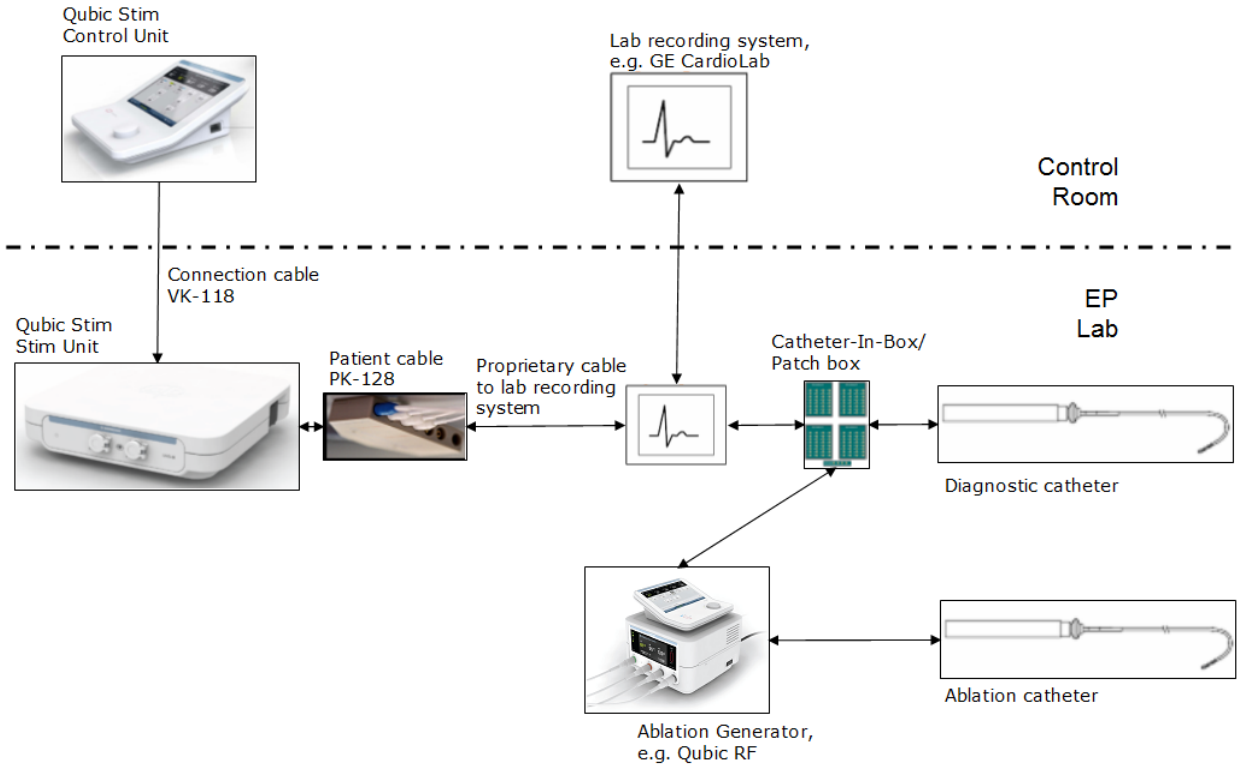

Fig. 1: Typical setting of electrophysiological examination and catheter ablation

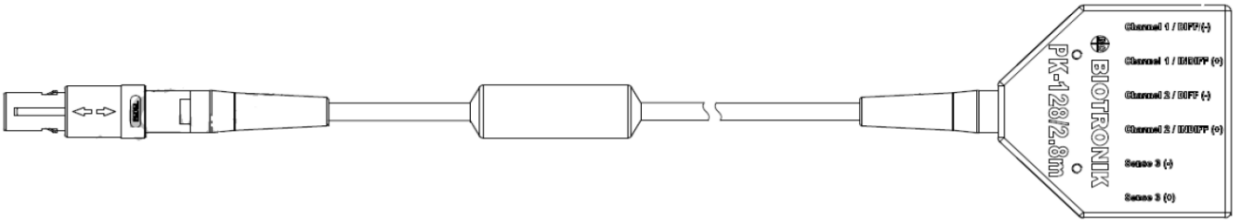

Fig. 2: PK-128 patient-end cable

6.2.2 Operating principle and action mechanism

Qubic Stim system is designed to provide the following stimulation modes:

- Programmed extra stimulation (PES) [1];
- Theta burst stimulation or high rate stimulation (Burst);
- Measurement of sinus node recovery tim (SNRT)

All parameters can be set on the control unit to control the device operation. The device is programmed and operated through the touch screen and other controls on the control unit. The whole operation of the system is controlled by software. The programmed stimulus plan can be saved and downloaded at an appropriate time.

6.3 Trial stretch

This Qubic Stim device is suitable for all patients who need cardiac electrophysiological examination which conducts diagnostic electrical stimulation on the patients during the examination. Therefore, the patients who have the indications of the intracardiac electrophysiological examination and are able to and willing to complete the intracardiac electrophysiological examination will participate in this trial.

[1] PES also means programmed extrastimulation, which specifically refers to adding extra stimulation to the heart rhythm to cause arrhythmia. Programmed extra stimulation is a more general term, including extra stimulation and other stimulation modes.

7 Indications, Contraindications and Precautions of the Product

7.1 Indications

The device is intended for diagnostic electrical stimulation of the heart, including induction and termination of tachyarrhythmia, refractory period measurements and electrical conduction measurements.

Qubic Stim stimulator has the following main functions:

- Programmed extrastimulation (PES)
- High rate stimulation (Burst)
- Measurement of sinus node recovery time (SNRT)

Qubic Stim is suitable for all patients receiving electrophysiological examination. Therefore, the medical indication of the device is the same as that of electrophysiological examinations which require or do not require catheter ablation for treatment.

7.2 Contraindications

Qubic Stim is not suitable for permanent and non-monitoring applications as an external pacemaker.

8 Overall Design

8.1 Trial design

8.1.1 Trial objective

It is intended to prove the clinical effectiveness and safety of Qubic Stim cardiac stimulator in Chinese population.

8.1.2 Selection of test method and reasons

A multicenter, prospective and single group method is adopted in this study. 106 subjects are selected from 3 study sites in China. The clinical evaluation of Qubic Stim stimulator and PK-128 patient-end cable provided by BIOTRONIK SE & Co.KG in accordance with MEDDEV 2.7.1 "*Guidelines for Clinical Evaluation of Medical Devices*" has well verified the safety and performance of the device. In addition, due to the mature design of the trial product, a single group of target values recognized by experts in the clinical professional field is used for evaluation. In a given clinical setting, the use of non-randomized design is acceptable.

8.1.3 Measures to reduce and avoid bias

In order to minimize and avoid the inherent bias of single group of target value design, the relatively objective and repeatable evaluation indexes are used in this study as the main evaluation indexes.

8.1.4 Investigational medical device

Components and models of investigational medical device

Name of Component	Model
Stimulus unit	Qubic Stim – EP Heart Stimulator
Control unit	Qubic Stim – Control Unit
Patient cable	PK-128

8.1.5 Subject selection

8.1.5.1 Inclusion criteria

The following inclusion criteria shall be met before patients are enrolled for cardiac electrical stimulation:

1. Age ≥ 18 years

2. Subjects who are willing to participate and sign the informed consent form，and are able to finish the follow-up at the study site.

3. Subjects with an indication of the intracardiac electrophysiological examination(fit one of the following):

- Paroxysmal supraventricular tachycardia: atrioventricular reentrant tachycardia or atrioventricular node reentrant tachycardia or atrioventricular tachycardia
- Ventricular arrhythmia: Premature ventricular contraction or ventricular tachycardia.
- Atrial fibrillation
- Atrial flutter

8.1.5.2. Exclusion criteria

1. Previous cases of unsuccessful radiofrequency ablation or recurrence
2. Pregnant and/or lactating women
3. Acute or severe systemic infection was present within 7 days prior to the intracardiac electrophysiological examination
4. Liver and kidney functions were obviously abnormal within 7 days prior to the intracardiac electrophysiological examination
5. Obvious bleeding tendency or blood system disease
6. Cancer and terminal disease
7. Combined with severe organic cardiovascular disease
8. Cerebral apoplexy and other cerebrovascular diseases within the past 3 months
9. Thromboembolic disease
10. Subjects who are participating in other interventional clinical trials

8.1.5.3. Criteria and procedures for termination of trial / trial treatment

When the study is completed or terminated, BIOTRONIK shall inform the investigators. Investigator shall return any investigational devices, equipment and relevant information they obtain at the request of BIOTRONIK. BIOTRONIK shall provide the final report to each study site. At the end of the study, BIOTRONIK will conduct a study closure visit, during which the BIOTRONIK shall verify the study records to ensure that the investigators can understand any applicable regulatory requirements, including those related to record keeping. After the date of termination or completion of the clinical trial, the investigators shall also keep the original documentation of the study for 10 years.

(1) Suspension or early termination of study

BIOTRONIK may terminate the study in advance or suspend the study due to the following circumstances:

BIOTRONIK monitors the safety after cardiac electrical stimulation by continuous evaluation of all adverse events related to cardiac stimulator. If serious adverse device events (SADE) affect the health and safety of the subjects, the study will be suspended until the cause of serious adverse device events is clarified. The study can only continue if the health and safety of the subjects are not affected. However, tachycardia events caused by any programmed stimulation will not cause the study to be suspended. Retraining is required if investigators fail to follow research protocols and regulations; if the investigator continues to fail to comply with the protocol and relevant regulations, the study will be suspended until the investigator is fully retrained and qualified.

In case of serious failure of investigational device due to cardiac electrical stimulation, all study sites shall immediately terminate the study.

(2) Follow-up requirements of subjects

After suspension or early termination of the study, the investigator must notify all subjects (who may not have completed the study). The study site will ensure that attention is paid to the subjects.

8.1.5.4. Enrollment time

106 cases are expected to be enrolled in this trial, and the enrollment is planned to be completed 3 months after the start of the trial. If the enrollment is not completed, the whole trial process will be postponed.

8.1.5.5. Expected overall duration of clinical trials and reasons for its determination

In this study, data is collected, analyzed and reported to further determine the clinical effectiveness and safety of Qubic Stim cardiac stimulator in Chinese population, which provides a basis for the application of pre-market approval.

All subjects who meet the inclusion and exclusion criteria will receive the intracardiac electrophysiological examination after signing the informed consent, during which the heart will be given diagnostic electrical stimulation through the Qubic Stim cardiac stimulator. The subjects will also receive the clinical follow-up after cardiac electrical stimulation until they are discharged from the hospital.

In view of the three-month enrollment time, the whole study is expected to start in October 2020 and end in Feburary 2021.

8.1.5.6 Predicted participation duration of each subject

Each subject can be enrolled only after signing the informed consent form. After that, the subject will receive cardiac electrophysiology in accordance with clinical routine diagnosis and treatment procedures as scheduled by the investigators. When the subject completes the follow-up on the day of discharge, the study will be ended.

8.1.5.7 Subject number required in the clinical trial

This study is a prospective, multicenter, single-arm, and interventional study with a sample size calculation for the main clinical observation indexes. In this trial, it is planned that 106 subjects will be enrolled.

8.1.6 Effectiveness evaluation method

8.1.6.1 Description of effectiveness parameters

Cardiac electrical stimulation is performed through the main function of the cardiac stimulator to achieve the corresponding expected clinical effect, which serve as the evaluation of clinical effectiveness.

8.1.6.2 Methods and time selection for evaluation, record and analysis of effectiveness parameters

The device is used for diagnostic electrical stimulation of the heart, including induction and termination of tachyarrhythmia, refractory period measurement and electrical conduction measurement. The main functions of cardiac stimulator include:

1. Programmed extrastimulation (PES)

   The expected clinical effect: the heart is effectively paced by PES at a set rate of stimulation.

2. High rate stimulation (Burst)

   The expected clinical effect: when the tachycardia is induced or terminated by high-rate stimulation, the device can effectively pace the heart at a set rate of stimulation.

3. Measurement of sinus node recovery time (SNRT)

   The expected clinical effect: the sinus node recovery time can be measured.

   The success rate of the Qubic Stim cardiac stimulator to send diagnostic electrical stimulation to the heart. The success standard refers to that all the main functions of the cardiac stimulator meet the success standards. Cardiac electrical stimulation is performed

by the above main functions of the cardiac stimulator in this trial, and when the above three functions in particular subjects are up to the standards, it is judged as stimulation success. The main evaluation index corresponds to the proportion of the patients who reach the success standards.

The target value for the success of this trial is defined as not less than 90%.

8.1.7 Safety evaluation method

8.1.7.1 Description of safety parameters

Serious adverse device events rate (P_{SADE}) is used in this trial to evaluate clinical safety of Qubic Stim cardiac stimulator.

8.1.7.2 Method and time selection for valuation, record and analysis of safety parameters

All adverse events shall be recorded throughout the study. However, only the serious adverse events that are definitely, likely or possibly related to Qubic Stim cardiac stimulator will become the basis of SADE event rate.

SADE related to Qubic Stim cardiac stimulator is defined but not limited to: serious adverse device events caused by failure to start-up, current failure to output, leakage current and other reasons. These will be recorded as SADE related to Qubic Stim cardiac stimulator. But in cases where electrical stimulation is known to cause potentially life-threatening arrhythmias, many times inducing these arrhythmias is the purpose of an electrophysiological examination. Therefore, any tachycardia events caused by programmed electrical stimulation in this study will not be included in SADE.

The important parameter P_{SADE} is the rate of serious adverse events that may be related to Qubic Stim cardiac stimulator for each subject, which is equal to the number of SADE divided by the number of subjects.

8.1.8 Other concerned data and evaluation indicators

In addition to collecting concerned data supporting predefined, subjects will be followed up until discharge after cardiac electrical stimulation, and further information will be collected at the same time, during which the follow-up data will be recorded on the CRF.

8.1.8.1 Adverse event

In addition to SADE, adverse events throughout the study shall be recorded and reported. The potential risks associated with the trial involve major complications of intracardiac electrophysiologic examination.

1. Arrhythmia: Atrial fibrillation is usually transient and does not require any treatment if there is no hemodynamic deterioration.If the subject is intolerant to atrial fibrillation, electrocardiography should be given. When ventricular fibrillation occurs, electrical defibrillation should be given immediately. Complete atrioventricular block occurs if the original bundle branch block is caused by another bundle branch block due to ablation or mechanical damage when the ablation catheter is near the site of the His bundle.

2. Pulmonary embolism: A clot forms in the sheath and rushes into the vein. The femoral artery and femoral vein were overpressurized and bandaged for too long. Prolonged bed rest after surgery, varicose veins in the lower extremities, old age, and hypercoagulability all contribute to venous thrombosis and pulmonary embolism in the lower extremities.

3. Systemic thromboembolism: Thrombus formation or thromboembolism may occur at the catheter entry site.

4. Vagus reflex: Pain, emotional stress, insufficient blood volume and other factors lead to strong reflex dilation of small blood vessels, resulting in decreased blood pressure and rapid slowing of heart rate.The operation time is too long, the fasting time is too long, stimulates the heart and the blood vessel wall; During the process of pulling out the indwelling sheath tube and pressing to stop bleeding, neck compression is too heavy or too long, which may cause vagal reflex.

5. Vascular complications: The formation of pseudoaneurysm means that the injury at the puncture site of the vascular wall cannot be closed, and the blood pressure enters the peripheral tissues to form a local hematoma. The formation of arteriovenous fistula is related to puncture.

6. Bleeding: Bleeding may occur occasionally, especially during femoral operations. The risk of bleeding increases when the femoral artery is used as the catheter approach, especially in obese people.

7. Infection: Invasive operation may lead to local infection of puncture, or in severe cases, systemic infection.

8. Acute pericardial tamponade: This causes hemopericardium if it causes a rupture of the blood vessels in the heart wall or pericardium.If pericardial tamponade is serious, pericardiocentesis for decompression is required.

In addition, the potential risk also involves the safety of the investigational device.Failure to comply with the investigational device safety regulations will not only cause harm to the subjects

and related personnel, but also damage the investigational device and other equipment. The following dangers may arise in the event of improper use:

1. Failure of important device functions
2. Personal endangerment due to electrical impact

8.2 Trial flow chart

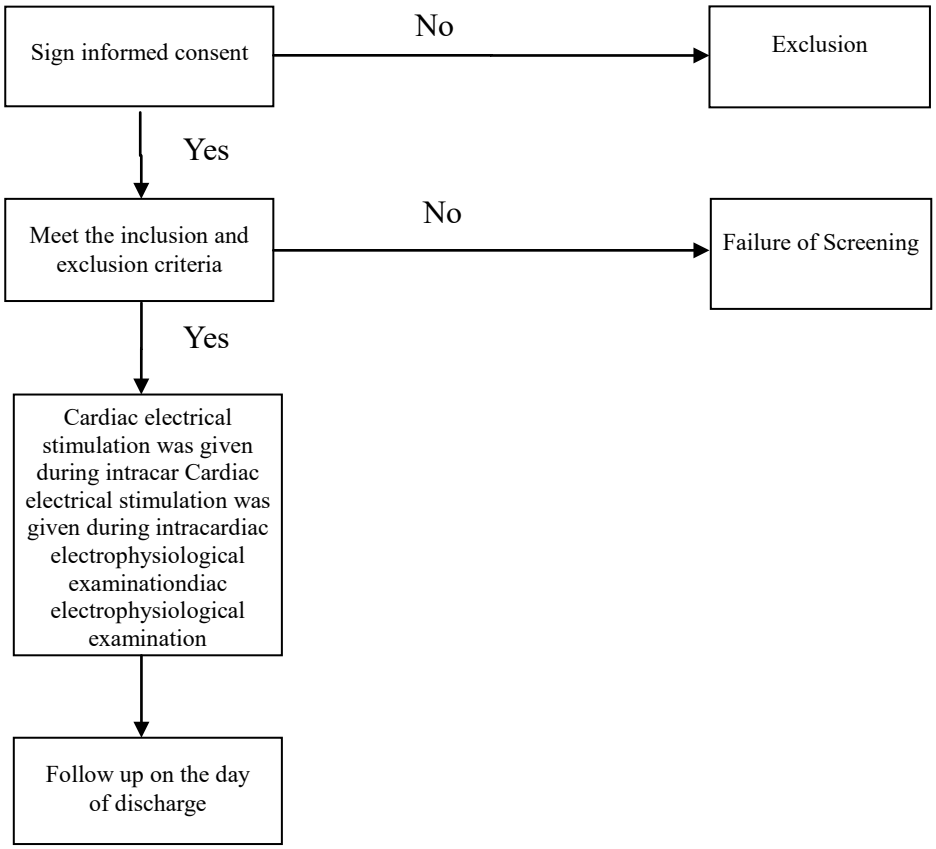

Fig. 3 Trial flow chart

8.2.1 Study follow-up plan

Specific follow-up in the study:

1. Baseline assessment
2. During the cardiac electrophysiological examination
3. Assessment on the day of discharge

Follow-up arrangement of the study: see Table 1 for details.

Table 1 follow-up arrangements of the study

Contents	Baseline assessment	Intracardiac electrophysiological examination	On the day of discharge
Obtaining informed consent (enrollment)	X		
Demographics, physical condition	X		
Indications of intracardiac electrophysiological examination	X		
Inclusion and exclusion criteria	X		
Drugs	X		
Cardiac electrical stimulation Keep the material related to cardiac electrical stimulation		X	
Evaluation of medical device		X	
Adverse event		X	X

1. Baseline assessment

Before enrollment, only subjects who sign the informed consent form and indicate the date are considered to be enrolled, and study-related procedures shall be carried out. The demographic data, indications of electrophysiological examination and medication situation shall be obtained and recorded.

All drugs taken by the subjects that may affect the cardiac pacing of electrical stimulation shall be recorded, including (but not limited to):

Class I – Flecainide and propafenone

Class II – β Receptor inhibitor

Class III – Amiodarone and sotalol

Class IV – Verapamil

2. Intracardiac electrophysiological examination

The electrophysiological examination was performed by person authorized by the investigators. Each study site shall use preset parameters (see Figure 4) to perform cardiac electrical stimulation, but for subject's safety, the investigator decides when to terminate the stimulation according to the specific condition of the subject during the operation. Investigators shall keep the materials related to cardiac electrical stimulation, such as downloading or printing the information of cardiac electrical stimulation by multi-channel analyzer.

Adverse events and device deficiencys during the electrophysiological examination shall be recorded.

First aid treatment shall be prepared at the site of cardiac electrophysiological examination, including extracorporeal defibrillators and all other basic first aid equipment and emergency measures for resuscitation / cardiac arrest / asystole.

Programmed extrastimulation (PES) (*: The extra stimulus S1S2S3S4 and S1S2S3S4S5 are optional)	
Incremental stimulus S1S1 (atrium or ventricle)	The circumference of the first stimulation is 400-600 MS (determined by the heart rate of subjects), decreased in 50ms, at a time until effective refractory period (ERP).
Extra stimulus S1S2 (atrium or ventricle)	S1: 400-600ms, circumference is determined according to the heart rate of the subject
	S2= S1-100ms (decreased in 10 ms until ERP)
Extra stimulus S1S2S3 (atrium or ventricle)	S1: 400-600ms, circumference is determined according to the heart rate of the subject
	S2: S1-100ms
	S3: S2-50ms (decreased in 10 ms until ERP)
Extra stimulus	S1: 500ms

S1S2S3S4* (atrium or ventricle)	S2: 500ms
	S3: 500ms
	S4: 300ms (decreased in 10 ms until ERP)
Extra stimulus S1S2S3S4S5* (atrium or ventricle)	S1: 500ms
	S2: 500ms
	S3: 500ms
	S4: 500ms
	S5: 300ms (decreased in 10 ms until ERP)
RS2 stimulus	S2=Sinus RR-50 ms (decreased in 10 ms until ERP)
High rate overspeed stimulation (Burst)	
High rate overspeed stimulation	300ms (at least 10 times)
Sinoatrial node recovery time (SNRT) 500ms (duration 30s)	
Parameter of Unified stimulus intensity Amplitude: 5.0 V, Pulse width: 2ms	

3. Follow-up on the day of discharge

Clinical follow-up shall be carried out on the day when the patient is discharged from the hospital in order to observe the short-term effects of electrostimulation for the heart. And all adverse events which have occurred since cardiac electrophysiology examination and until discharge shall be recorded.

4. End of the study

The study is completed after the subjects complete the follow-up on the day of discharge. For early termination of the study (e.g. quit, death), the cause and the date of last contact shall be recorded.

8.2.2 Device use specification

The authorized investigators can perform a cardiac electrical stimulation test. First aid treatment shall be prepared at the site of an endocardial electrophysiological examination, including external defibrillator and all other basic first aid equipment and emergency measures for resuscitation /cardiac arrest /asystolia.

8.3 Monitoring plan

As the sponsor of this study, BIOTRONIK is responsible for carrying out appropriate monitoring to ensure that this study can be conducted in accordance with the study protocol and relevant regulations.

BIOTRONIK shall ensure that the device is used under the direct guidance of the investigators. As investigators, the doctors shall comply with applicable laws and the stipulations of National Medical Products Administration, and implement the study in accordance with the signed study agreement and protocol and the requirements of Ethics Committee. Main investigators shall also assume the responsibility for all aspects of the study, including the work of other personnel involved in the study at the center.

The monitors shall be trained, qualified and appointed by BIOTRONIK to monitor the research progress of the study site. The monitors shall visit the study sites at regular intervals during the study. BIOTRONIK may also require company personnel to participate in the monitoring and follow-up process so as to assist the investigators. In regular monitoring, the evaluation of study site includes:

- Required CRF and other applicable research documents are completed and submitted.
- The study site can continue to be monitored.
- Clinical trial protocol is followed.
- Applicable laws and regulations on the responsibilities of investigators and record maintenance are followed

9 Statistical Considerations

9.1 Statistical design, methods, and analysis procedures

9.1.1 Study hypothesis

The study is a prospective, multi-center, single-group, and target-value-controlled clinical trial. The comparison with the target value proves that the test device meets the requirements of clinical application. The main endpoint index is the success rate of the Qubic Stim cardiac stimulator to send diagnostic electrical stimulation to the heart. The corresponding statistical hypothesis tests are:

$$H_0 : p_T \leq p_0$$
$$H_1 : p_T > p_0$$

Here, p_T represents the success rate of the test product; and p_0 represents the target value.

9.1.2 Statistical analysis methods

1) Descriptive analysis: Counting data is described by frequency and constituent ratio; while measurement data is described by mean, standard deviation, median, the 25th and 75th quantiles, maximum, and minimum.

2) Baseline demographic analysis: Descriptive analysis will be the main method. For subgroups comparison that may be involved, the likelihood data $\chi 2$ test will be used between counting data groups. When the theoretical frequency of more than 25% of the cells is less than 5, the Fisher exact probability method will be used. Grouped t-test is used for comparisons between groups with normally distributed measurement data; while Wilcoxon Rank Sum test used for comparisons between groups with non-normally distributed measurement data.

3) Efficacy analysis: All patients who use the investigational product will be included in the analysis. For the primary efficacy indexes, the asymptotic normal method and accurate probability method will be used to estimate the stimulation success rate and its 95% confidence interval, and the lower limit of the confidence interval are compared with the set target values to determine whether the test product meets the needs of clinical application. Meanwhile, the Tipping Point method will also be used to perform a sensitivity analysis on the potential impact of missing data. For the filled data, the asymptotic normal method and accurate probability method are also used to estimate the product success rate and 95% confidence interval, respectively. The statistical analysis method to be used for other efficacy indexes is the same as the baseline; for intra-group

comparisons that may be involved in specific indexes, paired t test is used for comparisons between groups with normally distributed measurement data; while Wilcoxon Rank Sum test used for comparisons between groups with non-normally distributed measurement data; and for intra-group comparison of qualitative indexes, the McNemar paired x^2 test is used.

4) Safety evaluation: Adverse events are described by the number and incidence of adverse events; meanwhile, the specific manifestation, severity and relationship between all the adverse events are described in detail.

5) For the main endpoint indexes, statistical analysis will be performed at a significance level of 0.025 on one side (corresponding to the one-sided confidence limit of the 95% confidence interval), and statistical analysis of other indexes will be performed at a significance level of 0.05 on both sides (unless otherwise stated). All the statistical analysis will be run on SAS®9.4 statistical software.

9.1.3 Statistical analysis procedures

Relevant links involved in the statistical analysis will be in accordance with the requirements in ICH E9 and the relevant requirements in the "*Guidelines for Biostatistics of Clinical Trials*" issued by the National Medical Products Administration (NMPA). Meanwhile, all statistical analysis processes will be performed in strict accordance with the Standard Operating Procedures (SOP) formulated by the Medical Statistics Department of the National Center for Cardiovascular Diseases.

9.2 Calculation of sample size

9.2.1 Total sample size

The total number of patients enrolled in this study is planned to be 106. The sample size is determined based on a combination of study hypothesis and estimates of expected levels of efficacy, and is calculated on a statistical basis. The sample size is calculated based on the primary endpoint index, *i.e.*, the success rate of Qubic Stim cardiac stimulator to send diagnostic electrical stimulation to the heart. Due to the limited reference materials for similar products, the "*Guidelines for the Technical Review of the Registration of Implantable Cardiac Electrode Lead Products*" combined with the opinions and recommendations of cardiac electrophysiological clinical experts, the target value of the primary index is set at 90%. Meanwhile, assuming that the expected success rate of the investigational product can reach 98%, when the significance level of the statistical test is 0.025 on one side, and the assurance level is 90%, considering the largest possible drop-out rate in the study

is 5%, and using the accurate probability method in combination, the sample size is finally set at 106 cases. The corresponding sample size calculation formula is:

$$n = \frac{\left[\mu_{1-\alpha}\sqrt{p_0(1-p_0)} + \mu_{1-\beta}\sqrt{p_T(1-p_T)}\right]^2}{(p_T - p_0)^2}$$

Here, p_T represents the predicted success rate level of the test product and p_0 represents the corresponding target value; μ represents the quantile corresponding to the standard normal distribution, α corresponds to the type I error level of the statistical test, and it is 0.025 here, while β corresponds to the type II error level of the statistical test, and it is 0.1 when calculation (corresponding to 90% power level).

According to the clinical practice, the estimated screening failure rate is expected to be 20%, so the estimated total number of screening cases is 133.

9.2.2 Case number of each disease in the clinical trial and the determination reasons

This trial protocol strictly limits the selected patients according to the inclusion/exclusion criteria. It can be considered that the current study is only conducted in patients with a single indication. The above 106 patients belong to the same disease group and will not be further divided.

9.2.3 The minimum and maximum subject numbers of each clinical trial institution in the multi-center clinical trial and the reasons

This trial will be conducted in multiple clinical trial institutions at the same time. In principle, the number of participants in centers will be distributed as evenly as possible to ensure sufficient center representativeness. However, considering the feasibility and actual progress of enrollment, the number of enrollment will be adjusted in accordance with the actual situation to ensure that the number of each center's participants is relatively balanced, and for a particular center, its final size should not exceed 50% of the total.

9.3 Significance level and power of the clinical trial

In this trial, the significance level and the power of the statistical test are 0.05 on both sides (except for otherwise stated) and the assurance degree of test is 90%, respectively.

9.4 Predicted drop-out rate

In the sample size design process, the largest possible drop-out rate in the study period is expected to be 5%. The drop-out includes all cases that ultimately cannot be included in the main analysis, and usually refers to significant violations of the study protocol judged by the principal

investigator. The possible situations include (not limited to): patients do not meet the inclusion/exclusion criteria; patients do not use any study-related products; patients use third-party products other than the study; patients do not complete follow-up as required; follow-up time windows exceed the set time limit; there are concomitant treatments that affect efficacy. All of the above will be included in the total drop-out rate.

9.5 Qualified/unqualified criteria of the clinical trial results

From a statistical perspective, judging whether the clinical trial results are qualified or not is equivalent to verifying the initial hypothesis. In this study, the primary evaluation index is the success rate of Qubic Stim cardiac stimulator to send diagnostic electrical stimulation to the heart. By comparing the trial results with pre-set target values, it is confirmed that the test product meets the clinical application requirements.

In summary, the determination of the trial results will be based on the comparison between the test product stimulation success rate and target value. If the results show that the lower limit of the 95% confidence interval of the test product success rate exceeds 90% (a preset target value), a positive result can be considered to indicate that the test product can meet the requirements of clinical application.

9.6 Criteria and reasons for terminating the trial for statistical reasons

This trial does not pre-set mid-term analysis and corresponding early termination criteria, so it is inapplicable here. All statistical analysis is performed after the data are collected, cleaned and finally locked.

9.7 Statistical methods for all data, including missing, unused and erroneous data (including halfway withdrawal by the subjects or the investigators) and treatment of unreasonable data

The statistical analysis process (procedure) is implemented in strict accordance with the Standard Operating Procedures (SOP) of the Medical Statistics Department of the National Center for Cardiovascular Diseases. Please refer to related documents for details.

For the missing data that may appear in the study process, the analysis will deal with the missing main efficacy indicators. The specific treatment methods will be explained in the statistical analysis plan. At the same time, we will also use Tipping Point critical point method for sensitivity analysis of the impact of missing data. For other missing indexes, we will analyze the data that are actually observed directly rather than by cut-off processing.

Erroneous and unreasonable data will be processed in the data cleaning process before statistical analysis. Information on patients who withdraw from the trial by themselves or by the investigators will still be included into the final statistical analysis. The statistical report will detail all the withdrawals by the patients or the investigators, and missing primary indexes resulting from early withdrawals will be treated according to the above treatment strategy for missing data.

9.8 Procedures for reporting deviation of original statistical plan

The statistical analysis proposal needs to be confirmed by the sponsor and the principal investigator, and finalized before the data are locked. Prior to finalization, the initial analysis plan can be modified in accordance with the actual situation during the trial. In principle, the main analysis principles, methods and analysis sets will not be modified, and all modifications will be recorded.

9.9 Criteria for selection of subjects incorporated into the analysis and its reasons

The statistical analysis will be performed on the basis of the following analysis populations, which will be clearly defined before the start of the statistical analysis. The analysis populations in this study include:

Full Analysis Set (FAS): An analysis set that is determined in accordance with the Intention To Treat principle, which will include all subjects who participates in the trial (recorded in the central registry) and do use the investigational product.

Per Protocol Set (PPS): refers to all subgroups of patients who have completed the trial without significant protocol deviation (referring to the study subject's violation of the inclusion/exclusion criteria, *etc.*).

The analysis of the primary efficacy indexes will be performed on the basis of the FAS and the PPS; all baseline demographic data and secondary efficacy analysis will be performed on the basis of the FAS, and the safety evaluation will also be based on the FAS. (So SS is not defined separately).

10 Data Management

10.1 CRF

Original data shall be collected from each study site, recorded in CRF and then verified by CRF.

10.2 Device data in CRF

All preset parameters of ECG stimulator shall be recorded in CRF, which can be downloaded or printed by multi-channel analyzer and saved as original data.

10.3 Data quality control

Biotronik shall verify the study data. At any time, Biotronik or the investigators approved by each study site shall report the completed and missing data. After CRF data is input into the database, the validity, consistency, deficiency and normal range of data shall be checked by the logic examination program. The data manager shall timely solve any problem discovered, those problems can be solved by making a judgment through comparing the data with that in other parts of CRF, as well as issuing data query table to the investigator.

11 Feasibility Analysis

11.1 Possibility analysis of success

The safety and performance of Qubic Stim electrical cardiac stimulator has been analyzed through the clinical evaluation report mentioned above, and it can be inferred that the trial results can be extended to ordinary Chinese patients.

Considering that the follow-up period is short and the subjects show good compliance, there will not be a large number of subjects lost to follow-up. Therefore, sufficient clinical data can obtained during the trial.

11.2 Analysis of failure possibility

The possibility of test failure involves: 1. The subjects fail to complete electrical cardiac stimulation test safely. 2. The cardiac stimulator cannot conduct pace-making and pace the heart or fail to measure the electrical conduction time. 3. The investigators fail to operate and collect data in accordance with the test requirements. In order to avoid test failure, the investigators shall be fully trained, the subjects shall be fully informed, and the study shall be conducted in strict accordance with the trial protocol.

12 Quality control of clinical trial

12.1 Monitoring of clinical trial

Study monitors are individuals who are appointed to be responsible for monitor the progress of study. The monitors are all properly trained and qualified to monitor the progress of clinical study. The study sponsor may appoint additional monitors at any time during the study. For additional information about the staff responsible for monitoring, please contact the sponsor.

The monitoring of the sponsor (or the representative) will visit each investigator prior to any procedure to ensure compliance with the following criteria:

The investigators understand and accept the obligation to conduct clinical study in accordance with the study protocol and applicable regulations, and hereby sign the clinical study agreement.

The investigators and their staff have sufficient time and facilities to conduct the study, and can access to a sufficient number of appropriate subjects for trial.

Original material shall be provided to prove the appropriateness of informed consent procedure, compliance with the study protocol, adequate reporting and follow-up of adverse events, accuracy of data collected in CRF and device information. The investigators/study site will be approved to access to such records. The study site shall maintain the signature log of monitoring visit. The investigators shall agree to take sufficient time to cooperate with the monitoring process and the investigators and/or study coordinator shall be present during the monitoring visit. The investigators shall provide the study supervisor with appropriate working environment for the purpose of reviewing study related documents.

12.2 Training

12.2.1 Study site training

All investigators/testing personnel shall participate in the training provided by the sponsor, which can be conducted in the form of investigator meeting, study site launch visit or other appropriate training form. Telephone training can also be carried out when necessary. The training for investigators/testing personnel includes but is not limited to protocol requirements, use of test equipment, filling in of EMR report form and responsibilities of testing personnel. All trained investigators/testing personnel shall sign a training log (or similar form) after training. Before signing the training log, the investigators/testing personnel shall not carry out any trial-related work beyond the treatment standards of the study site.

The investigators shall accept the training on device related knowledge organized by the sponsor.

12.2.2 Training for monitor of the sponsor

The sponsor and/or designated monitor shall accept the training on relevant protocol, CRF and use of test equipment (if applicable) and the training process will be documented in written procedure.

12.2.3 Support provided by the sponsor for the clinical trial site to be examined by the supervision department

If the supervision department contacts the investigators on matters related to this clinical trial, the investigators shall promptly notify the sponsor and inform the Ethics Committee as appropriate. During examination, the investigators and study coordinator shall be present to respond to reasonable requests and examination queries. The investigator shall provide the sponsor with a copy of all correspondence that may affect the inspection of this clinical trial (for example, observations and warning letters for inspection). The sponsor may provide any necessary assistance to the supervision department for examination.

13 Ethical issues and informed consent for the clinical trial

13.1 Ethic considerations

Clinical trial of medical device shall be carried out in accordance with ethical guidelines formulated in the Declaration of Helsinki of World Medical Assembly, GCP (Good Clinical Practice) for Medical Devices, and ISO14155. All parties involved in the clinical trial shall assume corresponding ethical responsibilities in accordance with their respective responsibilities in the trial.

13.2 Approval of trial protocol

This trial protocol does not need to be approved based on the provisions of State Administration for Market Regulation.

13.3 The process and text of informed consent

In accordance with the Declaration of Helsinki, GCP (Good Clinical Practice) for Medical Devices, and ISO14155, the subjects should sign the informed consent form prior to enrollment. Before the subjects participate in the clinical trial, the investigators shall fully explain the details of clinical trial, including known and foreseeable risks and possible adverse events, to subjects or

guardians of persons without or with limited capacity for civil conduct. After full and detailed explanation, the subjects or guardians thereof shall sign their names and the date on the informed consent, and the investigators shall also sign the name and date on the informed consent.

14 Provisions on reporting Adverse Events and Device deficiencys

14.1 Device deficiency

Device deficiency refers to unreasonable risks that may endanger human health and life safety in the normal use of medical devices during clinical trials, such as label errors, quality problems, faults, etc.

14.2 Adverse event

Adverse event (AE) refers to any adverse medical events, unexpected diseases or damages, and adverse clinical events (including abnormal laboratory results judged by physicians with clinically significant) related or not related with the investigational device which occurred in the trial process. AEs include all events related with the medical devices and surgeries.

During study, the symptoms presented by the subjects due to a pre-existing condition or condition prior to enrollment are not classified as AEs, for example, the attach frequency or severity kept unchanged.

The planned examinations that do not harm the health of subjects were not classified as AEs, e.g., regular cancer-preventive examination.

14.3 Adverse device events

Adverse device event (ADE) refers to adverse events related to the use of medical devices including all adverse events caused by the insufficient instructions for use, device application, installation, operations, or any function failures, as well as all adverse events caused by wrong use or intentional abuse use.

- Adverse Device Event (ADE): Adverse events caused or possibly caused by heart stimulator.
- Surgery-related ADE: Adverse events related or possibly related with surgical operations.

14.4 Serious adverse events

Serious adverse event (SAE) refers to adverse events occurring during the clinical trial which caused one of the following conditions:

- Death
- Serious aggravation of the health status, including:
  - Lethal diseases or damages;
  - Permanent defect of body structure or body function
  - Hospitalization treatment or prolonged hospital stays
  - Requiring medical or surgical intervention to prevent the permanent defect of body structure or body function;
- Fetal distress, fetal death, or congenital deformity, congenital defect, and etc.

The planned hospitalization before enrollment, surgeries required in the trial protocol, and events not causing serious aggravation of the health status are not regarded as SAEs. The medical or surgical interventions implemented to prevent the occurrence of life-threatening conditions are regarded as SAEs. For instance, the hospitalization due to pneumonia or hospitalization because of any surgical intervention is regarded as SAE. A new event occurring during hospitalization which prolonged the hospital stay (e.g., atrial fibrillation requiring cardioversion) is regarded as a new SAE, because two events had different diagnoses. The hospitalization before the aggravation of the health status (e.g., hospitalization due to the planned angiography) is not regarded as SAE.

14.5 Serious adverse device events

Serious adverse device event (SADE) refers to any adverse device events causing SAE consequences and characteristics.

Cardiac electrical stimulation-related SADE is the basis for the calculation of SADE rate endpoint. Endpoint-related SADEs including but not limited to serious adverse device events caused by failure to power on and output current, and current leakage, etc.

14.6 Unexpected adverse device events

All devices are subject to problems or breakdowns. Unexpected adverse device events (UADE) refers to any serious adverse events that threaten health or safety, or any life or death, caused by or related to a medical device, and the event, the problem, the nature of the death, the severity or extent of the morbidity has not previously been confirmed in the clinical trial protocol, or any other unexpected serious problems associated with the medical device detriment the subject's rights, safety or health. It is important to note that device failure due to product abuse is not considered an unexpected adverse device event.

14.7 Death of subject

If a subject died during the study, as much information as possible shall be obtained so that BIOTRONIK can report the details of the death.

If any, please provide the following available information:

- Cause of death
- Date and time of death
- Place of death
- Identify the heart rhythm at the time of death (if possible)
- Any other circumstances at the time of death
- Declare whether it is a device or operation related event
- The approximate time interval from the start of the event to death

14.8 Reporting procedures and contact information

- Regarding adverse events and device deficiency, the reporting procedures of all parties shall comply with the specific requirements of the "*Good Clinical Practice for Medical Devices*" (the State Food and Drug Administration's National Health and Family Planning Commission Order 25 of the People's Republic of China).
  - In the event of a serious adverse event in a clinical trial, the investigator shall immediately take appropriate treatment measures for the subject, and at the same time report in writing to the administrative department of medical device clinical trials of the affiliated clinical trial institution, and notify the sponsor in writing. The administrative department for clinical trials on medical devices shall, within 24 hours, report in writing to the relevant ethics committee and to the food and drug regulatory department and health and family planning department of the province, autonomous region or municipality directly under the central government where the clinical trial institution is located. In the event of death, the clinical trial institution and investigator shall provide the ethics committee and the sponsor with all required information.
  - For serious adverse events and may result in serious adverse events equipment defects, the sponsor shall, within 5 working days after receiving the record by the food and drug supervision and administration department and the health department in charge of family planning report, at the same level at the same time to participate in the test of other

institutions and researchers, clinical trial and its medical instrument clinical trial management department timely notify the clinical trial institution's ethics committee.

- Contact person of the sponsor: Lan Chen

  Tel:010-65223851

  E-mail: lan.chen@biotronik.com

15 Provisions for Deviations and Modifications of Clinical Trial Protocol

15.1 Deviations of Clinical Trial Protocol

The investigators shall conduct study in accordance with the study agreement and protocol. The investigators shall notify BIOTRONIK and the Ethics Committee within 5 days in writing of any significant deviation from the study protocol due to the protection of life or the maintenance of the subject's health in an emergency. Unless it is an emergency, significant deviations from the study protocol shall be approved by the BIOTRONIK in advance.

BIOTRONIK divides the cases of non-conforming study protocol into violation and deviation:

Protocol violations are cases of non-compliance with study protocol requirements and/or regulatory guidelines and are generally more serious in nature. The scientific reliability of the protocol and/or the rights, safety or health of the subject is potentially affected by protocol violations.

Protocol violations including but not limited to the following aspects:

- Without the consent of the subject
- Unauthorized investigators conduct clinical trials
- The enrollment criteria of subjects and protocol requirements were violated, which affected the important data of study design

The study site shall report the above situation to the Ethics Committee, fill out the protocol deviation form in the CRF, and provide a copy of the report submitted to the Ethics Committee to the BIOTRONIK.

Protocol deviations are deviations from study protocol requirements due to unavailability or inaccessibility of data.

The study site shall fill out the protocol deviation form in the CRF and submit it in accordance with the requirements of each Ethics Committee.

15.2 Modification of Clinical Trial Protocol

All modifications to the clinical trial protocol shall be submitted to the corresponding Ethics Committee for discussion and approval before implementation.

16 Direct Access to Source Data and Files

Originals or copies of all clinical results, observations and other activities throughout the clinical trial shall be recorded and kept in the medical history of each enrolled subject. For the data recorded on the CRF, the corresponding source data shall be shown on the medical history (source file).

The medical history (source file) shall include but not limited to the following information:

- Informed consent date
- Subjects participate in clinical trials
- Population characteristics
- Dated discharge report
- Medical history record and previous cardiovascular medications
- Records of cardiac electrical stimulation
- All adverse events: Diagnosis and symptoms, start and end dates, severity, measures taken, and prognosis
- Concomitant medication (cardiovascular medications)
- Completion or withdrawal date of clinical trial

17 Finance and Compensation

The sponsor of the trial is BIOTRONIK SE & Co.KG, and all expenses related to the study shall be provided by BIOTRONIK (Beijing) Medical Device Limited. If the subject is physically harmed due to the participation in this study, BIOTRONIK (Beijing) Medical Device Limited (on

behalf of BIOTRONIK SE & Co.KG) shall bear reasonable treatment costs and provide corresponding compensation in accordance with Chinese laws.

18 Content Covered by the Clinical Trial Report

The clinical trial report is consistent with the clinical trial protocol, which mainly includes the following contents:

General information; abstract; introduction; clinical trial purpose; clinical trial method; clinical trial content; clinical general information; investigational medical devices and predicate medical devices or predicate diagnosis and treatment method; adopted statistical analysis methods and evaluation methods; clinical evaluation criteria; organizational structure of clinical trials; description of ethical situation; clinical trial results; adverse events found in clinical trials and their treatment; analysis and discussion of clinical trial results, especially indications, scope of application, contraindications and precautions; conclusions of clinical trial; existing problems and suggestions for improvement; list of trial personnel; other situations that require to be explained.

19 Confidentiality Principle

The personal data of the subjects participating in the trial shall be kept confidential, but the Ethics Committee, the Medical Products Administration Department, the Health and Family Planning Administration Department or the sponsor may access the personal data of the subjects participating in the trial in accordance with the prescribed procedures when the work requires.

20 Agreement on Publication of Trial Results

The sponsor has exclusive ownership of the trial data and results. During the clinical trial, the sponsor has the right to access and use all data and results of the trial. Individual clinical trial centers are not allowed to publish and/or report their results until the results of all center are published and/or reported. The sponsor agrees that the leading investigators of the trial will publish the results of the clinical trial.

21 Duties of Parties

21.1 Duties of clinical trial institutions and investigators

Before the clinical trial, the clinical trial management department of medical devices of clinical trial institutions shall cooperate with the sponsor to submit an application to Ethics Committee and submit relevant document in accordance with the regulations.

Clinical trial institutions shall properly keep clinical trial records and basic documents as agreed with the Sponsor.

Investigators shall ensure that personnel involved in the trial are familiar with principles of medical devices for trial, scope of application, product performance, operational methods, installation requirements and technical indicators, understand pre-clinical research data and safety data of investigational medical devices, and master prevention and emergency treatment methods for risks generated in clinical trial.

Investigators shall ensure that all participants of clinical trial fully understand clinical trial protocol, relevant regulations, characteristics of medical devices for trial and duties related to clinical trial, sufficient subjects in clinical trial in accordance with inclusion criteria of clinical trial protocol, and enough time to safely conduct and complete clinical trial in accordance with relevant provisions within trial period agreed herein.

Investigators shall strictly obey clinical trial protocol and shall not deviate from the protocol or substantially change the protocol without consent of the sponsor and Ethics Committee or without approval of National Medical Products Administration. However, in case that subjects are under danger which are required immediately eliminated, it can also be reported in writing afterwards.

Investigators shall be responsible for recruiting subjects and communicating with subjects or their guardians. Investigators shall be responsible for explaining to the subject the details of the investigational medical device and clinical trial, informing subjects of potential benefits and known foreseeable risks, and obtaining dated informed content signed by subjects or their guardians.

The investigator or other personnel participating in the study shall not force or otherwise induce the subject to participate in the study.

In case investigators find adverse events unexpected for investigational medical devices in clinical trial, they shall modify relevant content of informed consent with the sponsor, and the affected subjects or their guardians shall resign on the modified informed consent for confirmation

after the modified informed consent is submitted to Ethics Committee in accordance with relevant working procedures for review and approval.

Investigators shall be responsible for making medical decisions related to clinical trial. In the event of adverse events related to clinical trial, clinical trial institutions and investigators shall ensure that adequate and timely treatment and management are provided to the subject. The investigator shall inform the subject of any complications that require treatment or management.

In case of serious adverse events in clinical trial, investigators shall take proper therapeutic measures for subjects immediately and report them to medical device clinical trial management department of clinical trial institutions to which it belongs in written form and inform sponsor of it in same way. Medical devices clinical trial management department shall report to the corresponding Ethics Committee, medical products administration department of provincial, autonomous region and municipality directly under the central government and Health and Family Planning Department where the clinical trial institution is located. In case of death incidents, clinical trial institutions and investigators shall submit all dossiers required to Ethics Committee and the sponsor.

Investigators shall record all adverse events and device deficiencys found in clinical trial process, jointly analyze causes of events with the sponsor, formulate written analysis report, give opinions on continuing, suspending, or terminating the trial, and report them to Ethics Committee for review through clinical trial management department of medical devices of clinical trial institutions.

Investigators shall ensure that clinical trial data are accurately, completely, clearly and promptly recorded in CRF. The CRF shall be signed by investigators. In case of any modification of data, CRF shall be signed and dated by investigators. Meanwhile original records shall be kept and clearly identifiable.

Clinical trial institutions and investigators shall ensure that data, document and records for clinical trial are authentic, accurate, accurate and safe.

The clinical trial institutions and investigator shall be subject to the sponsor's monitoring, verification, and the supervision of the ethics committee, and shall provide all required records relating to the trial. In case of medical products administration department and Health and Family Planning Department designate monitors to conduct inspections, clinical trial institutions and researchers shall cooperate.

In case that the clinical trial institutions and investigators find that risks may overweight the potential benefits or have obtained the result to judge safety and effectiveness of medical devices for trial, which requires suspension or termination of clinical trial, they shall inform the subjects, and ensure that subjects receive proper treatment and follow-up. At the same time, provide written explanation in details as specified, and report it to medical products administration department of the province, autonomous region or municipality directly under the central government where it is located if necessary.

Investigators shall promptly inform subjects after receiving notice of suspending or terminating clinical trial from the sponsor or Ethics Committee and ensure that they can receive proper treatment and follow-up.

In case that the sponsor violates the relevant regulations or requests to change the test data and conclusions, clinical trial institutions and investigators shall report it to medical products administrative department of the province, autonomous region or municipality where it is located or National Medical Products Administration.

At the end of the clinical trial, the investigator shall ensure that all records and reports are completed. Meanwhile, investigators shall ensure that numbers of investigational medical devices received conform to that of medical devices used, wasted and returned, and that the remaining experimental medical devices are properly disposed and documented.

The investigators may, in accordance with the needs of clinical trials, authorize relevant personnel to conduct recruitment of subjects, continuous communication with subjects, record of clinical trial data and management of the investigational medical devices, etc. The investigators shall conduct relevant training and develop appropriate documentation for their authorized personnel.

21.2 Duties of the Sponsor

The sponsor is responsible for initiating, applying, organizing, and auditing clinical trials, and is responsible for the authenticity and reliability of clinical trials. The Sponsor is usually a medical device manufacturer. In case that the Sponsor is an overseas institution, it shall have a designated agent in China in accordance with relevant provisions.

The Sponsor shall be responsible for formulating and modifying investigator manual, clinical trial protocol, informed consent, CRF, relevant standard operating procedure and other documents and organizing and conducting training required for clinical trial.

The sponsor shall select the testing institutions and investigators among the qualified investigational medical device clinical testing institutions in accordance with the characteristics of the medical device for testing. Before signing a clinical trial agreement with clinical trial institutions, the sponsor shall provide clinical trial institutions and investigators with the latest investigators manual and other relevant documents for their decision on whether to undertake this clinical trial.

Investigator manual shall include the following contents:

(1) Basic information of the sponsor and investigators;

(2) Overview of investigational medical devices;

(3) Summary and evaluation supporting intended use of investigational medical devices and rationale for clinical trial design;

(4) Declaration that the manufacture of investigational medical devices conforms to the requirements of the applicable medical device quality management system.

The Sponsor shall not exaggerate mechanism and effectiveness of investigational medical devices in clinical trial protocol.

During the clinical trials, when the sponsor receives important information affecting the clinical trial, the investigators' manual and related documents shall be revised in time, and submitted to the Ethic Committee for review and approval via the medical device clinical trial management department of clinical trial institutions.

The sponsor shall reach a written agreement with the clinical trial institutions and the investigators on the following items:

(1) The clinical trials are conducted in accordance with relevant laws and regulations and clinical trial protocols, and accept audits, verifications and inspections;

(2) The data recording and reporting procedures are followed;

(3) Basic documents relevant to clinical trial are kept no less than the legally-stipulated time, until the sponsor notifies clinical trial institutions and investigators that the documents are not necessary.

(4) After being approved by the Ethics Committee, the sponsor shall be responsible for providing the clinical trial institutions and investigators with the investigational medical device, and determining the transportation conditions, storage conditions, storage time, validity period, etc.;

(5) The investigational medical device shall be of qualified quality, easily identifiable, correctly coded and labeled with a special sign of “For trial”, and shall be properly packaged and stored in accordance with the requirements of the clinical trial protocol;

(6) The sponsor shall formulate the relevant standard operating procedures for the quality control of clinical trials, such as the transportation, reception, storage, distribution, treatment and recovery of the investigational medical device, which shall be followed by clinical trial institutions and investigators.

The sponsor is responsible for the safety of the investigational medical device used in the clinical trial. When it is found that the safety of the subjects may be affected or the implementation of the trial may change the approval of the Ethics Committee for continuing the trial, the sponsor shall immediately notify all clinical trial institutions and investigators and make corresponding treatment.

If the sponsor decides to suspend or terminate the clinical trial, it shall notify the clinical trial management department of medical devices of all clinical trial institutions within 5 days, and explain the reasons in writing. The medical devices clinical trial management department of clinical trial institutions shall timely notify the corresponding investigators and Ethics Committee. The suspended clinical trial shall not be resumed without the consent of the Ethics Committee. After the completion of the clinical trial, the sponsor shall inform the medical products administration department of the province, autonomous region or municipality where it is located in writing.

The sponsor shall ensure that all investigators implement the clinical trial strictly in accordance with the clinical trial protocol, and shall timely point out and correct any non-compliance of the clinical trial institution and investigators with the relevant laws and regulations, this Standard and the clinical trial protocol. In case that the situation become serious or persists, the clinical trial shall be terminated and reported to the NMPA and the medical products administrative departments of province, autonomous region or municipality directly under the central government where the clinical trial institution is located.

The sponsor shall bear the cost of treatment and corresponding economic compensation for the subjects who suffer injury or death related to the clinical trial, except for the damage caused by the fault of the medical institution and its medical personnel in the diagnosis and treatment activities.

The sponsor shall be responsible for the supervision of the clinical trial and selection of qualified supervisors to perform the supervision duties.

The number of supervisors and the time of supervision shall depend on the complexity of the clinical trial and the number of institutions participating in the clinical trial.

The supervisors shall have the corresponding professional backgrounds in clinical medicine, pharmacy, biomedical engineering and statistics and receive necessary training. The supervisor shall be familiar with the relevant laws and regulations and this specification, as well as non-clinical information of the investigational medical device and clinical information of predicate products, clinical trial protocol and relevant documents.

In order to ensure the quality of the clinical trial, the sponsor can organize monitors who are independent of the clinical trial and have corresponding training and experience to inspect the implementation of the clinical trial and evaluate whether the clinical trial meets the requirements of the trial protocol.

Inspection can be used as part of the routine work of clinical trial quality management of the sponsor, as well as to evaluate the effectiveness of the supervision activities, or to carry out verification for serious or repeated clinical trial protocol deviations, suspected fraud, etc..

For serious adverse events and device deficiency that may cause serious adverse events, the sponsor shall report to the filed medical product administration department and the health and family planning department at the same level within 5 working days after being informed, and shall also report to other clinical trial facilities and investigators participating in the trial, and timely notify the Ethics Committee of the clinical trial facility through the clinical trial management department of its medical device.

If the sponsor adopts electronic clinical database or remote electronic clinical data system, it shall ensure the clinical data controlled and true, and formulate complete verification documents.

For multicenter clinical trials, the sponsor shall ensure that documents are formulated before the clinical trials and that the responsibilities of the coordinator and other investigators are clearly defined.

For multicenter clinical trials, the sponsor shall develop standard operating procedures in accordance with the clinical trial protocol, and organize the training on the clinical trial protocol and the use and maintenance of the investigational medical devices for all the investigators participating in the trial, so as to ensure the consistency in the implementation of the clinical trial protocol and the use of the investigational medical devices.

In multicenter clinical trials, the sponsor shall ensure that the design of the Case Report Form is rigorous and reasonable, so that all data can be obtained by the coordinating investigator from each sub-center clinical trial institutions.

22 Statement of Investigators

Hereby I agree to:

1. The clinical trial shall be carried out in strict accordance with the declaration of Helsinki, the current regulations of China and the requirements of the trial protocol.

2. All required data shall be recorded in the Case Report Form (CRF) accurately and the clinical trial report shall be completed on time.

3. The investigational medical device is only used in this clinical trial. During the clinical trial, the reception and use of the investigational medical device shall be recorded completely and accurately, and the record shall be kept.

4. The sponsor is allowed to authorize or dispatch monitors, verifier, and regulatory authorities to monitor, supervise, and inspect the clinical trial.

5. The terms of the clinical trial contract/agreement signed by all parties shall be strictly performed.

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

Comments of the sponsor Signature (Seal) __ __,__(month/day/year)

Comments of investigators Signature __ __,__(month/day/year)

Comments of medical devices clinical trial institutions Signature (Seal) __ __,__(month/day/year)