

Clinical Trial Protocol for Medical Instrument

Perspective, multiple-centered, randomized control method evaluation
The safety and efficacy for clinical application of completely degradable occlusion system for ventricular septal defect

The Name of the Product: Completely degradable occluder system and surgical occluder intervention delivery devices

Model and Specifications: Refer to the main text of the protocol

Medical category of medical devices used in the trial:

Category III catalog of medical devices in need of clinical trial approval

Yes No

The same categories of products in China: Yes No

Medical Institute for clinical trial: Fuwai Hospital of Chinese Medical Science Academy

Serial Number/Date: XZKJ-1801-V1.0 / June 5th, 2018

Major researcher: Pan Xiangbin

Sponsor: Shanghai Shape Memory Alloy Co., Ltd

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1. The Information of the sponsor

- 1) The Name of the Sponsor: Shanghai Shape Memory Alloy Co., Ltd
- 2) The address of the sponsor: 41 building first floor, and fifth floor, No 258 Xinzhuan Highway, Songjiang High Tech Zone, Caohejing Development Area, Shanghai.
- 3). The contact way for the sponsor: Tele: 021-37013390

2. All the clinical research institutes and researchers list for multiple centered clinical trial

Clinical Trial Center Code	The Name of the clinical trial institutions	Researcher	Title	Contact way
01	Fuwai Hospital of Chinese Medical Science Academy	Pan Xiangbin	Chief Physician	010-68314466
02	The Second Xiangya Hospital of South China University	Zhao Tianli	Chief Physician/Professor	0731-85295601
03	Children's Hospital of Nanjing Municipality	Mo Xuming	Chief Physician/Professor	025-83117500
04	Hefei Gaoxin cardiovascular disease Hospital	Fang Weiyi	Chief Physician/Professor	0551-65376637

3. The purposes and contents for clinical trial

3.1. The Purpose of Clinical Trial

The purposes of the clinical trial is aiming at validating the safety and efficacy of completely degradable occluder system and occluder surgical intervention delivery devices manufactured by Shanghai Shape Memory Alloy Co., Ltd.

3.2. Content

The trial is “The clinical trial for safety and efficacy in clinical application of completely degradable ventricular septal defect occlusion system”, as a perspective, multiple-centered, randomized control non-inferiority clinical trial with the 6 month occlusion successful rate of completely degradable occluder after occlusion as the primary evaluation indices, and with the ventricular septal defect occluder and the occluder intervention delivery devices manufactured by the company as the control. It is

estimated that there are 108 cases (54 pairs) of subjects included in the 4 central groups nationwide between December, 2018 and December, 2019, during the treatment courses, it is randomly applied the completely degradable occluder system and occluder surgical intervention delivery devices manufactured by Shanghai Shape Memory Alloy Co., Ltd or ventricular septal defect occluder and occluder intervention delivery devices already marketed, and carry out clinical follow up instantly after operation, one month after operation, three months after operation, and six months after operation. After completion of 6 months clinical follow up, it is carried out clinical summarization, used in the registered application for products.

4. The Background Materials for Clinical Trial

4.1. Background Information

Ventricular Septal Defect (VSD) is one of the common congenital cardiac diseases, covering about 20% of all congenital cardiac diseases. In 2002, Amplatzer invented the Eccentric perimembrane ventricular septal defect occluder, and carried out clinical application in multiple countries of Europe, US and Asian, etc. Among them, the number of application in China is the maximum. Among the statistical early stage clinical trial cases with Complications of atrioventricular block unexpected occurred during early stage and follow up period after surgery, the ratio of cases in need of implanting artificial heart pacemaker reached 3.8%, even with the incidence about 4 years after operation. Since the peripheral VSD occluder with nickel-titanium membrane has shown the unexpected severe complication in clinical trial, in particular with the higher incidence of complete atrioventricular block, FDA in US has not yet ratified the clinical application for this model of occluder in US. Targeting at the insufficiency in the current occluder in application, Shanghai Shape Memory Alloy Co., Ltd autonomously developed the completely degradable occluder with Independent intellectual property rights, with the following characteristics:

- 1、 The raw materials of occluder are completely degradable, after complete endothelialization in the defect location after implanting, the occluder is gradually degraded without toxicity in the degraded products, capable of complete

- disintegration and absorption by human body, without adverse reaction and long term latent risks;
- 2、 It is avoided of the conduction block existed in NiTi alloy occluder; as well as the long term mechanical friction resulted in the injury to the peripheral tissues, even in aortic perforation, and valve damages;
 - 3、 It should be avoided of the fracture in the NiTi thread of occluder resulting in the injury and the puncture of the myocardial tissues, endocarditis, hydropericardium, and hemopericardium, fistula formation, and pericardial tamponade, etc;
 - 4、 Without Ni ion separation out caused by bioelectricity or body fluids, and blood corrosion, resulting in the Ni ion toxicity in patients, as well as the allergy in minority of patients to Ni ion and other issues;
 - 5、 Without potential risks caused by non-degradability of NiTi occluder in long term, such as the patients are in need of atrial septum or ventricular septum paracentesis, where there is a NiTi occluder formerly implanted. The degradable occluder can be completely degraded after implanting for 3 years, without residue, and the defect position is replaced by nascent myocardial tissue, which could be punctured after several years.

The completely degradable ventricular septal defect occluder is woven by poly p-dioxanone (PDO) thread, with formation, within the scaffolding framework, it is stitched with PLA Polylactic acid membrane, and the stitching thread is PDO wire.

PDO is a kind of aliphatic polyester with excellent biocompatibility, bioabsorbability, and biodegradability. In its molecular chain, there is unique ether bonds, endowed it with excellent flexibility, suitable to be processed into thread materials, which is advantageous for weaving. As the absorbable suturing thread, the degradation of PDO is started from about 6 months, and basically degraded at 12 months, first, it is hydrolyzed from high molecular into large molecular, and then gradually degraded into small molecular, which are engulfed by cells into tricarboxylic acid cycle, and turned into acetone, finally degraded into carbon dioxide and water. As the absorbable suture wire, PDO has been approved by FDA in US long since 2004 (US J&J as absorbable suture), and in 2011, Chinese Tianjing Hensheng absorbable suturing

thread has also gained the approval by CFDA in China, and widely applied in various operations in general surgery, orthopedics, gynaecology, urology, hepatological surgery, etc, as well as the suturing and ligation of organs, subcutaneous tissues, and muscles. Since 2015, absorbable intraocular micro tube plug made from PDO pipe materials has been approved by FDA in US, to use in the treatment of eye dryness. Since 2011, blood vessel hemostatic clips made from PDO materials have been applied in the ligation closure for blood vessels in laparoscopic operation (Hangzhou Shenshi Science and Technology, absorbable blood vessel clips, as shown in Figure 2). Practice demonstrate, the materials are excellent in biocompatibility, without rejection, without complications.

Poly(lactic acid) (PLA) is amorphous polymer, with glass transition temperature between 50 and 60°C. Poly(lactic acid) degradation is divided into two steps, first, it is hydrolysis, PLA under the effects of body fluids (water), the copolymer bonds break, and the mechanical strength of materials reduce, and then the long chains are changed into short chains, until it is degraded into small molecular lactic acid monopolymer. And then it is enzymolysis, with small molecular lactic acid participated in the Tricarboxylic acid metabolism, and then generate into carbon dioxide and water, and discharge out of the body through the respiration and excretory system. The materials can be used as the medical surgery anti-sticking mucosal membrane, micro gel capsule for injection, micro bead and embedding agents, etc as the adjuvant of controlled release formulations, at the same time it can be used as porous brackets and skeletal fixation or tissue repairing materials for tissue engineering cell cultivation such as: Surgical operation suture thread, implanting pieces and artificial skin, artificial blood vessel, retina in ophthalmology, etc, after approval by FDA. The finished medical products with poly(lactic acid) as the raw materials include, Bio-fix company in Finland, Grand fix absorbable bone pegs and suturing thread in Japan, Johnson suturing thread in US, and SurgiWrap degradable anti-sticking mucosal membrane in US, etc.

4.2. Preclinical Trial Research Conditions

We have passed through the in vitro experiments and animal experiments, to carry out assessment for the biological safety, compatibility, and feasibility as well as efficacy of the degradable occluder.

In order to put the degradable occlusion system into clinical application as promptly as possible, and benefit the broad congenital heart diseases patients, it is now applied for the human body clinical trial research for the clinical validation of the efficacy and safety of new products, to gain the approval for the registration certificate of the products and marketing approval.

The current trial selected ventricular septal defect occluder and occluder intervention delivery devices manufactured by Shanghai Shape Memory Alloy Co., Ltd (refer to as Shanghai Shape in the following) as the clinical trial control products.

The model and specification already approved for marketing of ventricular septal defect occluder are as following: SQFDQ-IIi 04、SQFDQ-IIi 05、SQFDQ-IIi 06、SQFDQ-IIi 07、SQFDQ-IIi 08、SQFDQ-IIi 09、SQFDQ-IIi 10、SQFDQ-IIi 12、SQFDQ-IIi 14、SQFDQ-IIi 16.

The occluder intervention delivery devices model and specifications already approved for marketing are as following:

Models	Specifications
Type I	5F、6F、7F、8F、9F、10F、12F、14F
Type II	5F、6F、7F、8F、9F、10F、12F、14F
Type III	5F、6F、7F、8F、9F、10F、12F、14F
Type IV	5F、6F、7F、8F、9F、10F、12F、14F

Completely degradable occluder system and occluder surgical intervention delivery devices have been registered for inspection in the testing institutions recognized by SFDA and Quality Technological Monitoring Department of the State Council, with the testing results as eligible. Completely degradable occluder system registration inspection reports: SFDA Jinan Medical Instrument Quality Monitoring Inspection Center Inspection Report, with serial number as: Y2015092510;

The occluder surgical intervention delivery devices registration inspection report: Z-Y-0437-2018

The completely degradable occluder system and occluder surgical intervention delivery devices manufactured by the company have met all the conditions required by the current clinical trial research, with less expected adverse reaction for the products at present, however it cannot be obliterated of the possibility for adverse reaction during application of the

products.

5. Product Characteristics, Structural Compositions, Working Principles, Operating Mechanism, Model and Specification and Trial Scope

5.1. Product characteristics

The completely degradable ventricular septal defect occluder is woven by poly p-dioxanone (PDO) thread, with formation, within the scaffolding framework, it is stitched with PLA Polylactic acid membrane, and the stitching thread is PDO wire, both of which are completely degradable materials. Through specific processing technique, to ensure the occluder degradation is in match with the endothelialization, according to the animal experiment results:

- At one month, occluder products woven by PDO thread materials are started for endothelialization, and the HE staining demonstrated PDO thread materials have almost no changes;
- At three month, occluder products woven by PDO thread materials are finished for endothelialization, and the HE staining demonstrated PDO thread materials have basically no changes;
- At 6 months, HE staining demonstrated PDO thread materials started degradation;
- At 9 months, PDO thread materials are further degraded;
- At 12 months, PDO thread are mostly degraded, and left with the hollow cavity;
- At 24 months, the hollow cavity left by PDO thread degradation have gradually been filled with the growth of myocardial tissues;
- At 36 months, the hollow cavity after degradation have been completely filled by myocardial tissues.

5.2. Product Structure Composition, Working Principles, Operating Mechanisms

The completely degradable occluder system includes the degradable occluder, loader, delivery devices and safety rope.

Completely degradable occluder is woven by PDO (sealed with polyactic acid choke flow membrane), demonstrated as stretched stripes after pulling by strength, after the removal of which, it can automatically restore to over 80% of the formation shape. After regulation by safety rope, it can restore to original shape. Such performance ensures that the occluder can

firmly fix on the defect positions after it is in place. The performance of formation of stripe shape after pulling can pass the occluder through the occluder surgical intervention delivery devices into cardiac defect positions. The polyactic acid membrane in the occluder plays the role to choke the blood flow, after the implanting of occluder, it shall completely close the defects, to realize the purposes of healing the atrial septal defects.

The type of degradable occluder is thread materials woven type. The shape design is shown in Figure 1.

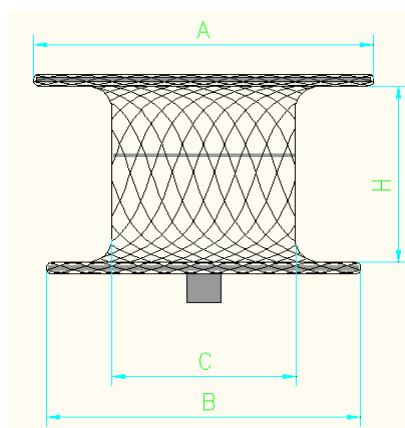


Figure 1. Type IIIIIIIVV diagrams of completely degradable occluder

H—The total height of the occluder A—The diameter of upper disc B—The diameter of lower disc C—Waist Diameter

Among them the type of loading devices is catheter type. The shape design is shown in Figure 2.

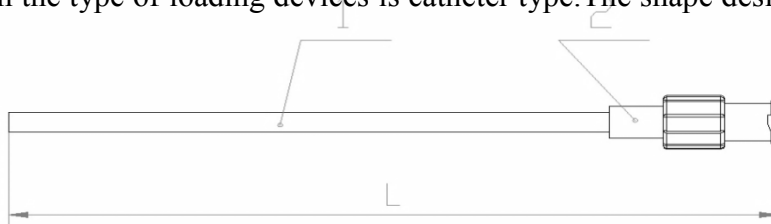


Figure 2. Loader Diagram

1. Loader sheath 2. Loader connector L is the length of loader

Among them the type of delivery devices is of clamp type. The shape design is shown in



Figure 3.

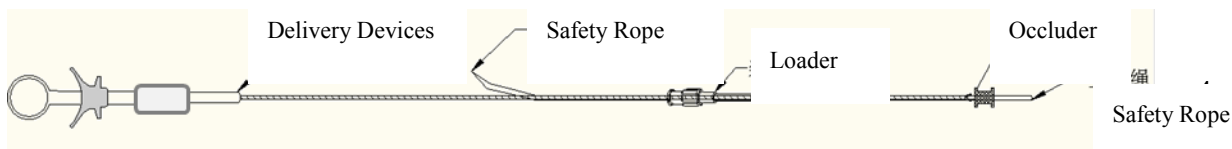
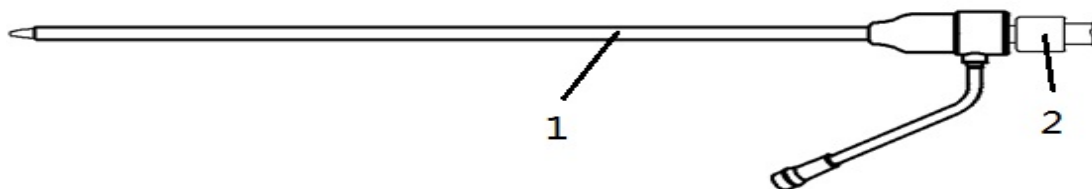


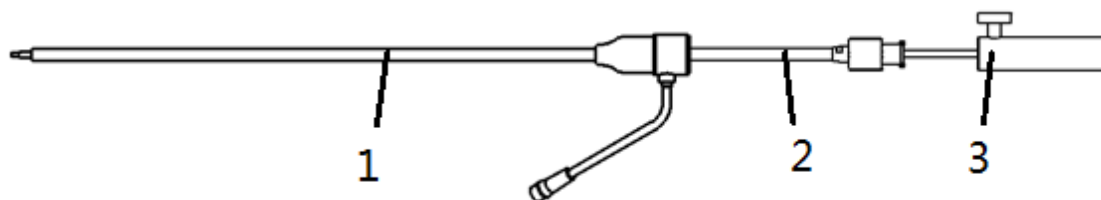
Figure 4. The complete design diagram of completely degradable occluder system

The occluder surgical intervention delivery devices are consisted of outer sheath, expander, loader, delivery device, guiding wire, and two way valve.



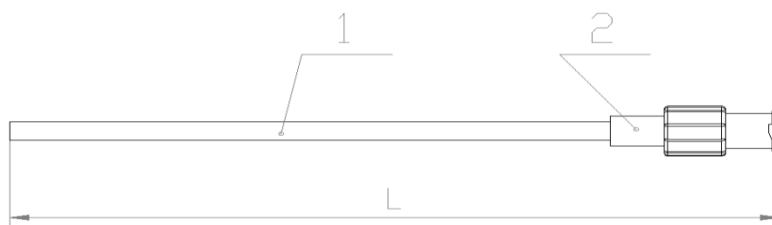
1. Outer sheath 2. Expander

Figure 5. Outer sheath and expander outfit



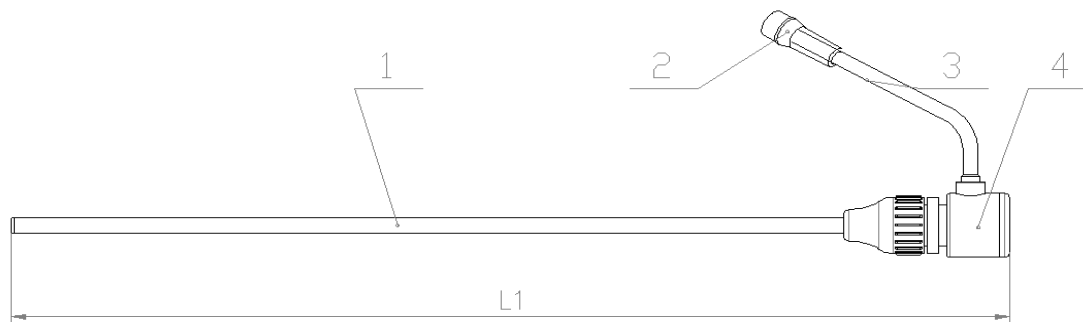
1. Outer sheath 2. Loader 3. Delivery Device

Figure 6. Outer sheath, loader and delivery device outfit



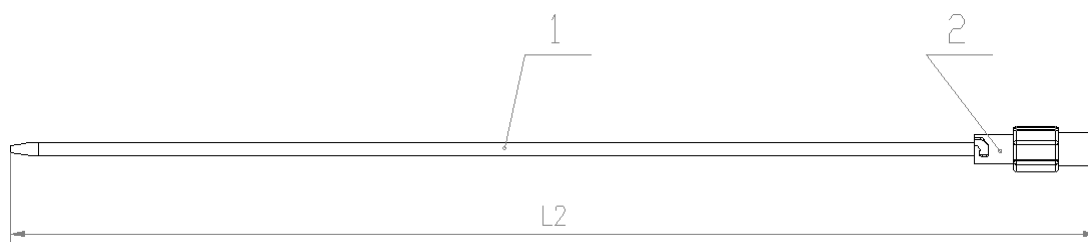
1. Loader sheath 2. Loader Connector

Figure 7. Loader Structure Diagram



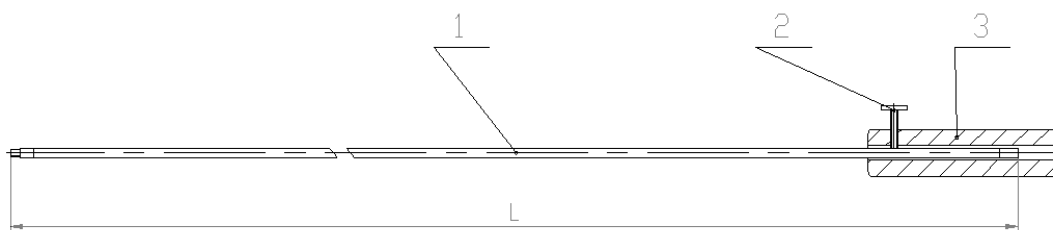
1. Outer sheath 2. Standard luer taper 3. Extension Tube 4. Hemostatic Valve Connector

Figure 8. Outer Sheath Structure Diagram



1. Expanding tube 2. Expander connector (the inner hole is standard luer taper).

Figure 9. Expanding Tube Structure Diagram



1. Delivery rod 2. Fixing Screw 3. Rotational Handle

Figure 10. Delivery Rod Structure Diagram

5.3. Test Scopes

The test scopes of completely degradable occluder system: The current product is applied in the treatment of ventricular septal defect in congenital cardiac diseases;

The occluder surgical intervention delivery devices are dedicated in the surgical intervention operation, and they are used in the delivery of various occluders manufactured by the company into the lesion location for release. It is applied in the occlusion treatment for the atrial septal defects, ventricular septal defects and patent ductus arteriosus.

6. Products Indications and Contraindications, and matters in need of attention.

Indications:

Completely degradable ventricular septal defect occluder is a type of percutaneous ventricular

septal defects closure devices through catheter, used in the ventricular septal defects with abnormality of hemodynamics or enlargement of left ventricular inner diameter.

Contraindications:

- 1). Patients with moderate to severe resistant type pulmonary arterial hypertension.
- 2). There exists thrombus in the cardiac cavity. There is hemorrhagic diseases, such as active ulceration.

Matters in need of Attentions:

- 1). The degradable occluder system and occluder surgical intervention delivery devices have already been sterilized before discharge.
- 2). The product is disposable product, forbidden for application after resterilization after opening.
- 3). If it is discovered of the opening, damages, leakage of packages or over the sterilization validity period, please do not use it.
- 4). The selection of occluder delivery sheath is crucial, such defects as unmatched between the sheath tube and the occluder, may result in the delivery and withdrawal difficulty, even result in the blood vessel injury.
- 5). The product is only limited to the application by the physician already receiving occlusion technique trainings.
- 6). It is necessary to prepare for the emergency conditions, and withdraw the thrombus devices that may severely influence the flowing property of blood.
- 7). For allergic patients with polyactic acid, and poly (p-dioxanone), they may have allergic reaction for the product.
- 8). The product is applicable for MRI.
- 9). In order to avoid the adverse outcome, please read the manual carefully before application, in particular, it must take heed of all precautions and matters in need of attention.

7. General Design

7.1. Trial Design

7.1.1. Testing purposes

The purpose of the clinical trial is aiming at validating the safety and efficacy of completely degradable occluder system and occluder surgical intervention delivery devices manufactured

by Shanghai Shape Memory Alloy Co., Ltd, through the current clinical trial research.

7.1.2. Trial Method Selection and Their Rationale

The current trial applied perspective, multiple centered, randomized controlled non-inferiority clinical trial. It is evaluated of the safety and efficacy of completely degradable occluder system in clinical application, with the ventricular septal defect occluder manufactured by Shanghai Shape Memory Alloy Co., Ltd as the clinical trial control product. It is evaluated of the safety and efficacy of occluder surgical intervention delivery devices in clinical application, with the occluder intervention delivery devices manufactured by Shanghai Shape Memory Alloy Co., Ltd as the clinical trial control product. The primary endpoint index for evaluating occluder surgical intervention delivery devices is that it can be released when the occluder is delivered to the lesion location during operation; and the primary endpoint index for evaluating completely degradable occluder system is the success rate at month 6, which is evaluated for efficacy through ultrasonic cardiogram.

7.1.3. Measures for reduction and avoidance for deviation.

- 1) Before research initiation, the sponsor should carry out relevant training for researchers participated in the current research, and ensuring that the researchers sufficiently understand the research flow, and skillful in the operation of research instruments; during the course of research, the researchers should carry out operation strictly according to the operating methods and specification in the research protocol, and the clinical research monitor should do well of the quality control and monitoring work, and ensure that the researchers carry out operation and implementation strictly according to the research protocol. It is implemented of the measures mentioned above during the entire research procedures, to reduce the losses or operation errors;
- 2) It applied strict randomized trial design, to avoid the selection deviation in treatment. After the trial started, when the subjects meet the inclusion criteria for testing, the researchers shall log on to the central randomizing system for randomized grouping.

- 3) Subjects are screened for inclusion and exclusion strictly according to the clinical diagnostic criteria in trial protocol, to reduce the selection deviation;
- 4) Application of independent data management and statistical analysis shall be conducive to reduce the trial errors. When the clinical trial is completed, do well of data management and sorting work, when data issues shall arise, the data analyst shall carry out data check up through data questioning table, and avoid the record errors.

7.1.4. Medical devices used in trial and medical devices used in control

Testing Instrument: Completely degradable occluder system manufactured by Shanghai Shape Memory Alloy Co., Ltd.

Models and Specifications: ABFDQ-I-04, ABFDQ-I-05, ABFDQ-I-06, ABFDQ-I-07, ABFDQ-I-08, ABFDQ-I-09, ABFDQ-I-10, ABFDQ-I-12, ABFDQ-I-14, ABFDQ-I-16, ABFDQ-II-04, ABFDQ-II-05, ABFDQ-II-06, ABFDQ-II-07, ABFDQ-II-08, ABFDQ-II-09, ABFDQ-II-10, ABFDQ-II-12, ABFDQ-II-14, ABFDQ-II-16, ABFDQ-III-04, ABFDQ-III-05, ABFDQ-III-06, ABFDQ-III-07, ABFDQ-III-08, ABFDQ-III-09, ABFDQ-III-10, ABFDQ-III-12, ABFDQ-III-14, ABFDQ-III-16, ABFDQ-IV-04, ABFDQ-IV-05, ABFDQ-IV-06, ABFDQ-IV-07, ABFDQ-IV-08, ABFDQ-IV-09, ABFDQ-IV-10, ABFDQ-IV-12, ABFDQ-IV-14, ABFDQ-IV-16, ABFDQ-V04, ABFDQ-V05, ABFDQ-V06, ABFDQ-V07, ABFDQ-V08, ABFDQ-V09, ABFDQ-V10, ABFDQ-V12, ABFDQ-V14, ABFDQ-V16

Instrument in control: Ventricular septal defect occluder manufactured by Shanghai Shape Memory Alloy Co., Ltd.

SQFDQ-IIi 04、SQFDQ-IIi 05、SQFDQ-IIi 06、SQFDQ-IIi 07、SQFDQ-IIi 08、SQFDQ-IIi 09、SQFDQ-IIi 10、SQFDQ-IIi 12、SQFDQ-IIi 14、SQFDQ-IIi 16

Testing Instrument: Occluder surgical intervention delivery devices manufactured by Shanghai Shape Memory Alloy Co., Ltd.

Models and Specifications: 5F、6F、7F、8F、9F、10F、12F、14F

Control Instrument: Occluder intervention delivery devices manufactured by Shanghai Shape Memory Alloy Co., Ltd.

Models and Specifications:

Models	Specifications
Type I	5F、6F、7F、8F、9F、10F、12F、14F
Type II	5F、6F、7F、8F、9F、10F、12F、14F
Type III	5F、6F、7F、8F、9F、10F、12F、14F
Type IV	5F、6F、7F、8F、9F、10F、12F、14F

7.1.5. Selection of subjects

7.1.5.1. Inclusion Criteria

- (1) The subjects and (or) their legal guardians should know the nature of the current research, and consent to participate in the current clinical trial according to all the clauses of the current research. They must sign the informed consent approved by the ethics commission, and agree to receive the post-operative treatment protocol, and finish the follow up and relevant inspection required by the follow up, according to the follow up requirements.
- (2) Aged between one year and 60 years old, with body weight higher than 10kg, male or not pregnant women;
- (3) Effective shunt mouth for VSD is between 3mm and 14mm;
- (4) The upper margin of VSD is no less than a distance of 3mm from the right coronary valve of aorta, without aortic right coronary valve shedding into VSD and aortic regurgitation above moderate degree;

7.1.5.2. Exclusion Criteria

If there is any of the following condition, the current subjects should be excluded from the participation in the clinical trial:

- (1) Irreversible pulmonary blood vessel diseases; Severe pulmonary artery hypertension accompanied by shunts in double directions;
- (2) Hemorrhagic diseases or blood coagulation dysfunction already known (including thrombocytopenia resulted from heparin), with contraindications against platelet treatment, or possible of rejection for blood transfusion;
- (3) Septicemia or severe infections within one month before occlusion operation;
- (4) There exists thrombus in the location of occluder, and patients with venous thrombosis at the insertion point of the catheter;
- (5) Cardiac deformity patients survived with VSD;
- (6) Patients deemed by the researcher as inappropriate for the application of the current

product

7.1.5.3. Standards and Procedures for the stop of trial/test treatment

Falling off standard:

All the subjects filling out the informed consent and qualified in screening for enrollment into randomized research, when they withdraw from the trial research in any time for any reasons, so long as they failed to accomplish the observation cycle prescribed by the protocol, they shall be deemed as falling off cases, and stop the trial. Common falling off causes include:

- (1) Occurrence of serious adverse events resulted in the furthering completion of the trial;
- (2) Changes in diseases conditions, unsuitable for furthering completion of the trial;
- (3) Loss of follow up;
- (4) The patients or their family members demanding withdrawal from the trial;
- (5) Incapable of furthering completion of the trial for any other reasons;
- (6) The subjects are poor in compliance, influencing the efficacy and safety judgment.

After the subjects' falling off, the researcher must contact the subjects for all possibilities, and ask for the reasons and accomplish all the assessment items possible of completion. When the patients withdraw due to the allergic reaction, adverse reactions, and invalid treatment, the researchers must adopt the corresponding treatment measures according to the actual conditions of the subjects.

Rejecting Criteria:

All the cases already included however comply with any of the following conditions, must be rejected:

- (1) Misdiagnosis (without application of any testing instrument);
- (2) Patients without any testing records (without application of testing instrument);
- (3) Patients incompliance with the inclusion/exclusion criteria (without application of testing instrument);
- (4) Due to the application of any forbidden drug, which results in the incapability for effective evaluation (without application of testing instrument).

For rejection cases it must be explained for the reasons, and their CRF Table must be preserved and ready for review. Without treatment statistical analysis, however after receiving

treatment, with at least one effectiveness and safety records, the patients can participate in the safety analysis according to conditions.

Standards/Procedures for the stop of trial/test treatment:

When adverse events occur, the clinical trial personnel must make clinical judgment in time, and take measures to protect the subjects' rights and interests; when necessary, the ethics commission has the right to terminate the clinical trial; for termination of clinical trial, it should be informed of the subjects, sponsor, ethics commission and SFDA, and explain the reasons.

Before terminating the clinical trial in advance, it should be informed of the medical institutions, ethics commission and SFDA, and explain the reasons.

7.1.5.4. Grouping Time

Before eligible for inclusion, it is necessary for the agreement by the subject and sign the informed consent, and then carry out inspection:

- 1) General data of subjects, and vital signs;
- 2) Past treatment history, clinical diagnosis and past treatment;

If it complies with the inclusion criteria of the current research rather than the exclusion criteria, after making preparation before the treatment, it shall take the occluder implanting time by surgery as the grouping time point.

7.1.5.5. Expected overall sustainable time for clinical trial and its determination reason

Adoption of NiTi alloy woven for VSD occluder with VSD occlusion operation has been widely applied for over one decade, and the operating techniques and clinical follow up research have been very mature, the completely degradable occluder in the current trial has not been changed in the basic structure, operating mechanism for VSD occluder compared with the traditional VSD occluders.

According to the past products already received the registration certificate and their application already proven their safety, literature references both home and abroad are generally taking 6 months as the limits for short term efficacy evaluation of occluder, and the residual shunts after occluder implanting are mainly concentrated in the first 3 months after operation. Animal trial research demonstrate, the occluder has already been in complete endothelialization within 3 months after occluder implanting, taking into account of the long term observation for validity and safety of products after implanting into human body, therefore, the current clinical trial selects 6 months as the follow up time for clinical trial.

7.1.5.6. Expected participating sustaining time for each subject

The duration from the subjects signing the informed consent, grouping, operation to follow up completion are about 7 months, and the primary endpoint for follow up completion as the conclusion of the trial, and it is further follow up to 3 years after trial completion.

7.1.5.7. Subject number necessary for clinical trial

It is expected of 108 subjects for inclusion, respectively of 54 cases in the trial group and control group.

7.1.6. Effective Evaluation Method

I. Effective parameter explanation

Primary Efficacy Indices: 6 months occlusion success rate.

6 months occlusion success (definition): 6 months occlusion success refer to ultrasonic cardiogram inspection in follow up 6 months after operation, there is no residual shunts in the occlusion location or only with minor amount of residual shunts.

Secondary Efficacy Indices: Surgical Technical Successful Rate.

Surgical Technical Successful Rate (Definition): Surgical intervention delivery devices through the occluder (trial group) or occluder intervention delivery devices (control group) implanting the occluder and then safely released.

Secondary Efficacy Indices: Technical Successful Rate.

Technical Successful Rate (Definition): Surgical intervention delivery devices through the occluder (trial group) or occluder intervention delivery devices (control group) implanting the occluder and then safely released, without occluder shedding during operation.

II. Evaluation, recording and analysis of effective parameter method and time selection

Immediate, 1 month, 3 months, 6 months occlusion success after intervention occlusion operation, namely ultrasonic cardiogram suggesting the residual shunt bunch diameter no higher than 2mm, according to the Doppler shunts signal from left to right judgment, it is better in effect to have no shunts signal from left to right; with diameter lower than 1mm from left to right shunts signal as trace amount of residual shunts; with diameter between 1 and 2mm as minor amount of residual shunts.

7.1.7. Safety Evaluation Method

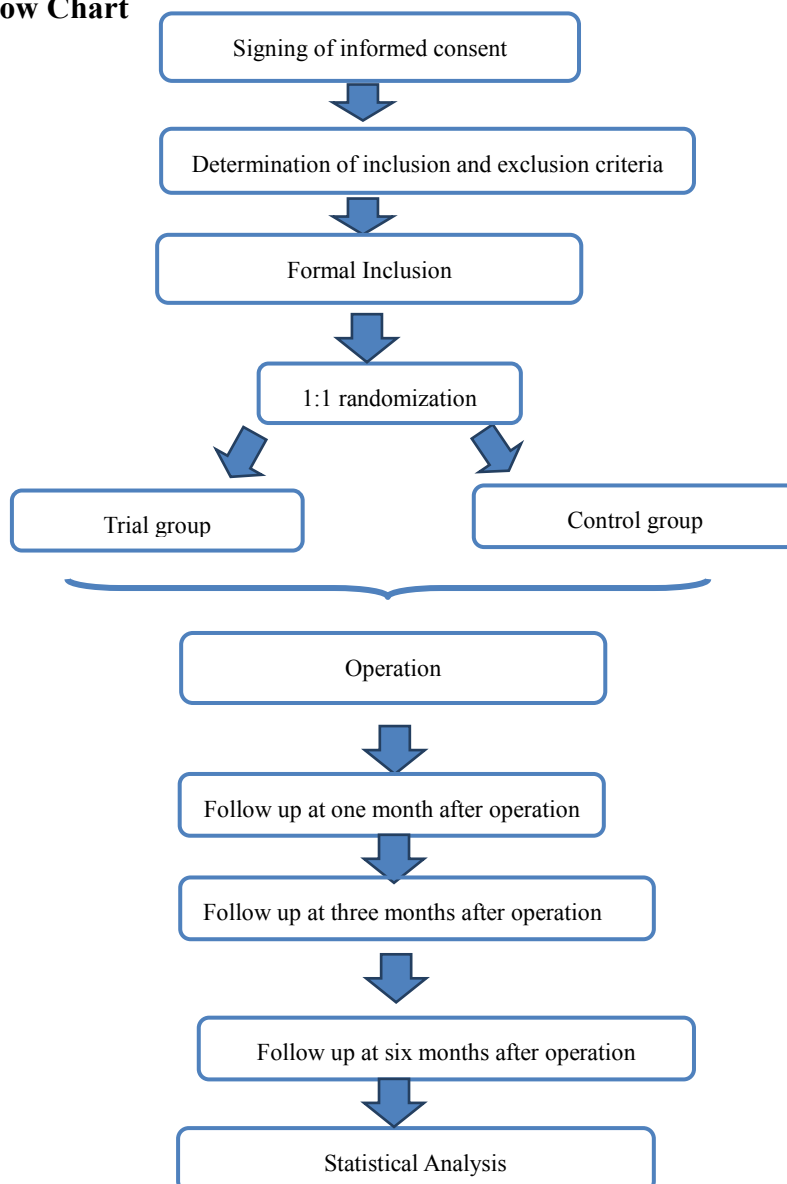
1 month, 3 months, 6 months after operation, it is mainly recorded of the severity, incidence date, duration time, treatment and results for all the adverse events and serious adverse events by clinical symptom safety and adverse event assessment.

The method and time selection for evaluation, recording and analysis of safety parameter: the monitoring of subjects' vital sign including before operation, during operation, and before discharge; adverse events monitoring including during operation, immediately after operation, before discharge and follow up for safety.

7.2. Trial Procedure

- Written informed consent shall be signed.
- Check up of exclusion criteria
- Case Inclusion
- Intervention operation (intervention operation and implanting occluding devices)
- Follow up evaluation

I. Trial Flow Chart



II. Trial Flow Chart

Research Stages	Screening	Treatment/follow up period					
	<i>Pretreatment</i>	<i>Hospitalization Treatment Period</i>			<i>Follow up 1</i>	<i>Follow up 2</i>	<i>Follow up 3</i>
Time window	Before operation Within 15 days	Operation Record:	Immediately after operation.	Between Post operation and pre-discharge	1 months ± 7 days	3 months ± 15 days	6 months ± 30 days
Informed Consent	√						
Inclusion/Exclusion Criteria	√						

Demographic Data	√						
Vital Signs	√	√		√			
Medical History	√						
Medication Record (History)	√	√	√	√	√	√	√
Blood Routine:	a			√			
Urine Routine	√ ^a			√			
Blood Biochemistry	√ ^a			√			
Blood coagulation	√ ^a						

Urine Pregnancy	√ ^a						
Electrocardiogram	√ ^a	√	√	√	√	√	√
Ultrasonic Cardiogram	√ ^a	√	√	√	√	√	√
Chest X-rays	√ ^a			√			
Adverse Events		√	√	√	√	√	√

a. If the blood routine, urine routine, blood biochemistry, blood coagulation, urine pregnancy, electrocardiogram, Chest X-rays, ultrasonic cardiogram have already been carried out within 15 days before signing of informed consent, they can serve as baseline assessment, needless of repetition; for urine pregnancy, it is only necessary for women of child bearing age.

b. Medication records are only necessary for recording of anti-coagulation, anti-biotics and anti-virus drugs relevant to trials;

For testing items not required by the current protocol however with relevant prescription in the medical institutions, it is carried out of inspection according to the requirements in details of the medical institutions.

7.3. Operation Procedure and Instrument Application Norm

7.3.1. Preparation before operation

It is prepared according to the cardiac surgical operation.

7.3.2. Implanting Procedures

Systemic anesthesia trachea cannula, operation area sterilization, routine operation list. Make a skin incision of a length between 2cm and 3cm subcostal, sequentially incise the skin, subcutaneous tissues and muscle layer, and partly cleave the sternum, cut open the pericardium and suspend, to expose the right ventricle, and suture a pad type pouch on it. Puncture the puncturing needle through the center of the pad, send the guiding steel wire into the cardiac cavity, make sure that the guiding steel wire is through the VSD, and then withdraw the puncturing needle, deliver the delivery sheath along the guiding steel wire through the VSD, withdraw the delivery sheath inner core and the guiding steel wire. Select the occluder of proper diameter according to the measuring results, in general the selected occluder diameter is 2 to 4 mm larger than the defect diameter detected with ultrasonic measurement. Load the occluder into the loading sheath, discharge all the air bubbles in the occluder through the side hole on the hemostatic valve. Connect the loading sheath with the delivery sheath, deliver the occluder, during the operation, it is used of esophagus ultrasonic cardiogram real time monitoring, open the left ventricular side umbrella disc, make the occluder umbrella into plane shape, withdraw it to the left ventricle opening of the defect, and fix the delivery device, withdraw the sheath, release the occluder right ventricle side umbrella disc. Push and pull the occluder back and forth, if the location is fixed, the ultrasonic inspection detected occluder would not influence the aortic valve, tricuspid valve and the neighboring tissue structure, release the delivery device tong head, and release the occluder. Since the degradable occluder is woven by degradable high molecular materials, the elasticity is inferior than the common NiTi alloy occluder, after complete release, it can only restore to about 70% of the original form, therefore, it is necessary to pull the safety rope, and contact the lower disc surface of the occluder with the outer sheath tube mouth, through pulling the safety rope, restore the occluder completely into the original form. Finally, withdraw the safety rope, release the delivery device handle dead lock piece, release the occluder, and withdraw both the delivery devices and outer sheath from the heart.

7.3.3. Instrument Application Norm

(1). Research group Instrument

Name: Completely degradable occluder system;

Manufacturing unit: Shanghai Shape Memory Alloy Co., Ltd

Storage Conditions: Stored in temperature lower than -10C, without corrosion gas and in clean environment.

Validity Period: One year

The Name: Occluder surgical intervention delivery devices

Manufacturing unit: Shanghai Shape Memory Alloy Co., Ltd

Storage conditions: The current product shall be stored in cool, dry, clean, well-ventilated environment without corrosive gases, and it shall be avoided of direct sun glaring and rain and snow falling during transportation procedures.

Validity Period: Three years

(2). Control group Instrument

The Name: Ventricular septal defect occluder (Product already registered by Shanghai Shape Memory Alloy Co., Ltd);

Manufacturing unit: Shanghai Shape Memory Alloy Co., Ltd

Storage conditions: The current product shall be stored in clean environment with relative humidity no higher than 80%, without corrosive gas, dry and well-ventilated.

Validity Period: Three years

The Name: Occluder intervention delivery devices (Product already registered by Shanghai Shape Memory Alloy Co., Ltd).

Manufacturing unit: Shanghai Shape Memory Alloy Co., Ltd

Storage conditions: The current product shall be stored in dry, clean, well-ventilated environment without corrosive gas.

Validity Period: Three years

(3). Package

The packages from inside to outside are respectively: Blister box, double layer dialysis bag (Paste with label on the second layer), alumina foil bag (Paste with label on the surface).

(4). Label

- ① The Name and Address of the sponsor
- ② Identify inner content and package operation batch no and/or codes

- ③ “Used in Clinical Trial” mark
- ④ Storage Requirements
- ⑤ Application time limits (Expiry Date)

(5). Instrument Preservation and Management

All the instruments used in the current research shall be preserved in the clinical research trial unit, which shall establish strict testing instrument preservation and distribution registration system, and dedicated personnel by the sponsor shall directly deliver the testing instruments into the various research center, and the research center shall establish sophisticated trial instrument receiving procedures with the implementer, and the record shall include: Date, Quantity, Batch No/Serial No, Expiry Date, etc.

The sealed instrument package shall be preserved under prescribed temperature and humidity conditions, each research unit shall select the instrument manager, and establish the dedicated “Application Record Form for clinical trial medical instrument”, and register the subjects’ name Pinyin abbreviation, and randomized no, application date, and signature by the instrument manager, etc.

The trial instrument can only be taken for application by the authorized research personnel. Each instrument taken out from the preservation location shall be recorded and signed by the research personnel. Only sealed instrument package can be returned into the cabinet, and make the corresponding records.

After trial termination the trial sponsor shall collect all the unused instrument, and responsible for the recovery of unused research instrument and carry out centralized processing. When the research finishes, it should be counted of all the materials.

(6). Application Instruction

It should be applied of the instrument according to the prescription in compliance with the suggestion by the company in the current protocol. In order to avoid the adverse outcome, please read the manual carefully before application, in particular, it must take heed of all precautions and matters in need of attention.

The product is applicable for MRI.

7.4. Monitoring Planning

Monitoring Frequency: First case monitoring, for each 5 cases of patients grouped shall be monitored once; at the same time, since the grouping of the first case of patient, it shall be monitored routinely for every 3 months.

Monitoring content:

- ① Confirm the subjects according to the inclusion criteria for grouping;
- ② Check up the CRF according to the original medical history of the subject and original records and research medical history, to ensure the accuracy of the records, which should be in time and integral;
- ③ Inspect the researcher's document folder in the center, to ensure that the content shall be integral without mistakes;
- ④ It shall be inspected of the trial operation to be complied with the protocol, as well as the requirements in GCP;
- ⑤ It shall be inspected that the trial is carried out of operation according to the requirements by the ethics commission;
- ⑥ It shall be inspected of the procedure norm for acquisition of informed consent;
- ⑦ If the above content is deviated from the protocol, formulate the protocol breach report and submit to the ethics commission.

8. Statistical Consideration

8.1. Statistical Design, Method and Analysis Regulation

8.1.1 Statistical Design (Hypothesis Inspection)

The current trial adopts perspective, multiple centered, randomized control design and the comparing type is non-inferiority trial. Through the comparison with the similar products already marketed, it has been proved that the trial instrument can meet the clinical application needs in the same way, and for the primary evaluation index, it is setup as the occlusion successful rate 6 months after implanting in evaluation during operation, and the corresponding statistical hypothesis inspection is :

$$H_0 : p_T - p_C \leq -\Delta$$

$$H_1 : p_T - p_C > -\Delta$$

In the equation p_T , it corresponds to occlusion successful rate 6 months after implanting in the trial group, and p_C represents the occlusion successful level 6 month after implanting in the control group, Δ represents non-inferiority limit value (here it is positive value).

8.1.2 Statistical Analysis Method

- (1) Description analysis: The counting data were described with frequency number and composing rate; and the measurement data applied mean value, standard deviation,

maximum value, minimum value, as well as the median value, 25 and 75 percentiles.

- (2) Baseline demographic statistical analysis: On the basis of descriptive analysis, between the counting data groups, it applies continuous calibration χ^2 inspection, when the unit block theoretical frequency number over 25% is lower than 5, it applies the Fisher's Exact Test; for normal distribution, the comparison between different counting data groups, it applies grouping t Test; for abnormal distribution, it applies Wilcoxon Rank and Wilcoxon Rank Sum Inspection for comparison between groups.
- (3) Efficacy Analysis: For occlusion successful rate 6 months after implanting as the primary efficacy indices, it applies the adjustment of central effect with CMH Chi-square test as the method to compare between different groups, apart from the assessment for the successful rate between trial and control groups, it should also be assessed for the difference value between successful rate in different groups as well as 95% confidence interval. For other efficacy indices, the comparison method between groups is similar as the baseline analysis. For within group counting data comparison with normal distribution, it applies matched t Test; for within group counting data comparison with abnormal distribution, it applies Wilcoxon Sign Rank Test.
- (4) Safety Evaluation: Describe the case number of normal before treatment and abnormal after treatment and their percentage respectively according to the test group and control group. Described the adverse events with the case number of adverse events and their occurrence, and carried out continuous calibration χ^2 test or Fisher precision probability method test. At the same time, it shall be described in details of the embodiment for all adverse events, their degrees and relevance with the research products.
- (5) For primary efficacy indices, the statistical analysis shall be carried out under the significance level with 0.025 on single side (which correspond to 95% confidence interval on one side confidence limit), for other indices, all the statistical analysis

shall be carried out under significance level with 0.05 on both sides (excluding specifically annotated otherwise).It applies SAS[®] 9.4 statistical software for statistical analysis.

8.1.3. Statistical Analysis Regulation

Relevant links involved in the statistical analysis shall all comply with the prescription in ICH E9, as well as the relevant requirements in the “Biological Statistical Guiding Principles in Clinical Trial” released by CFDA. At the same time, all the analysis procedures shall all be strictly implemented according to the Standard Operation Procedures (SOP) released by Medical Statistical Department in National Cardiovascular Diseases Center.

8.2 Sample Volume Calculation

8.2.1 Total Sample Volume

It is expected of 108 cases of patients included in the trial, randomized into the trial group or control group with the ratio of 1:1, with 54 cases in each group. The calculation of sample volume is based on the primary evaluation indices, namely the 6 months occlusion successful rate after implanting.

In combination of the current clinical evidence and experience assessment by the clinical experts, it is assumed that the 6 months occlusion successful rate is about 98% after implanting in patients of the control group, it is expected the trial products in the trial group in application can also reach the same successful rate level, it is determined by clinician and sponsor after joint discussion that the non-inferiority limit value is set as 8%, when the significance level for statistical test takes 2.5% on single side, with test power of 80%, taking into account of the maximum incidence of 10% falling off rate and randomized block length in the research, according to statistical principles, it is calculated that, for each group, it is necessary for 54 cases of patients inclusion, total case number in both groups are 108 cases.

The corresponding sample volume calculation equation is:

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

In the equation p_T correspond to the 6 months occlusion successful rate after implanting in trial group, and p_C represents 6 months occlusion successful rate after implanting in control group; $\bar{p} = (p_T + p_C)/2$ is average successful rate between both groups; Δ corresponds to non-inferiority limit value; μ represents the percentile of standard normal distribution, α corresponds to Type I error level for statistical test, which is 0.025 here, while β corresponds to Type II error level for test, when calculated, it takes 0.2 (corresponding to 80% of test power).

8.2.2 Case Number of each diseases in clinical trial and their determination reasons

There is strict restriction for inclusion and exclusion standards for recruited patients in the trial protocol, it can be considered that the current research is carried out with the target of patients with individual indications, and the 108 cases mentioned above all belong to the same disease category, not necessary for further division.

8.2.3 The minimum and maximum subject number in each clinical trial institution and their reasons

The current research shall be carried out in multiple clinical research institutions at the same time, in principle, it shall be evenly distributed into the various center grouping as much as possible, to ensure the sufficient center representativeness. However taking into consideration of the feasibility and inclusion schedule, it would carry out adjustment for the inclusion number in all the participated unit according to the actual conditions, to ensure the balance of inclusion scale for each center, while for a specific center, the final inclusion scale shall be no more than 50% of the total cases number.

8.3 Significance level and Test Power for Clinical Trial

In the current trial, the significance level for the statistical test shall take 5%(on both sides)(unless specified otherwise), and the test power take 80%.

8.4 Expected Falling Off Rate

In the sample volume design procedures, it is expected that the maximum possible falling off rate during research period shall be 10%, which include all the conditions that cannot be included into final major analysis, it is generally referred to severe breach against the research

protocol (influencing the major efficacy evaluation) judged by the major researchers. The including conditions are: The patients do not comply with the inclusion criteria; the patients fail to use any research related products; the patients use the third party products during research; the patients fail to complete follow up according to prescription; or it is accompanied by treatment influencing efficacy, etc. All of the conditions mentioned above shall be counted into the overall falling off rate.

8.5 Eligible/Ineligible Criteria of Clinical Trial Results

From statistical angle, it is judged of the eligibility and ineligibility of the trial results, correspond to the validation for initial hypothesis inspection. For the current research, the primary evaluation index is the 6 months occlusion successful rate after implanting, and the comparison type of the trial is non-inferiority inspection, which is planned to be proved through trial result. Compare the trial group and control group product, they both have the same treatment efficacy.

In conclusion, the judgment of trial results shall be based on the difference between the occlusion successful rates in the trial group and the control group, if the results demonstrate: The occlusion successful rate in trial group subtracting that in control group in the lower limit of 95% confidence interval is greater than -8% (the non-inferiority limit value setup in advance), it can be explained as non-inferiority conclusion is established. Otherwise, the non-inferiority conclusion can not be reached.

8.6 Standard and Reasons for termination of trial based on the statistical

The current trial has no pre-set up middle term analysis and early termination standard correspondingly, therefore, it is inapplicable here. All the statistical analysis shall be carried out after the completion of data gathering, cleaning and final lock up.

8.7 Data statistical method, in combination with missing, unused or wrong data (including withdrawal and termination mid term) as well as the processing method for unreasonable data.

Statistical analysis procedures are implemented strictly according to the Standard Operation Procedure (SOP) by the medical statistical department of National Cardiovascular Disease Center. For details, please refer to relevant documents.

For missing data that may occur during research procedures, during analysis, it shall carry out cutting and transfer targeting at the missing of primary efficacy indices, for the cutting and

transfer method in details, it shall be explained in the prospectus for statistical analysis. In general, it applies single value cutting and transfer method such as LOCF (Last Observation Carry Forward) strategy or WCCF (Worst Case Carry Forward) strategy to carry out processing for the missing data in the primary indices. For the occurrence of missin data in other indices, it would not carry out cutting and transfer, instead it is carried out of analysis for data actually observed.

Wrong and unreasonable data shall be screened during the data screening procedures before statistical analysis. For mid term withdrawn or terminated of the trial, the data of this part of patients shall be included into the final statistical analysis. In the statistical report, it would carry out in detail explanation for the causes of withdrawal or termination patients, for missing data resulted from early stage withdrawal, it should be cutting and transferred according to the missing data processing strategy mentioned above.

8.8 Reporting Procedures Deviated from the original statistical plan

The statistical analysis prospectus is in need of the confirmation by the sponsor and the major researcher, and finalize before the database lock up. Before finalize, it can be modified of the initial analysis prospectus targeting at the actual conditions in the trial procedure, in principle, it would not modify the major analysis principles, methods and analysis set, and all the modification shall be recorded.

8.9 Selection Standard and Causes for subjects included into the analysis

Statistical analysis shall be based on the foundation of the following analysis population, before the initiation of statistical analysis, it would make clear definition for the analysis population, which include:

Full Analysis Set (FAS): The subject set defined according to the Intention To Treat Principle, referred to the data set of all the subjects participated in randomization and applying research devices. For patients fail to observe of the primary efficacy indices, it is planned to apply WCCF (Worst Case Carry Forward) strategy to carry out cutting and transfer for the missing data.

Per-protocol population set (PPS): Refer to all the treatment population subgroup finished the trial and excluded the severe breach of protocol (refer to research subject breaching the inclusion criteria or in compliance with the exclusion criteria, etc).

The primary efficacy indices analysis shall be carried out on the basis of Full Analysis Set and Per-protocol population set at the same time; in addition, all the baseline demographic data and secondary efficacy analysis shall be carried out on the basis of Full Analysis Set, and the safety evaluation shall also be carried out on the basis of Full Analysis Set (Therefore, it would not define SS separately).

8.10 During validation of hypothesis, it is excluded of specific information and their causes (if applicable)

Not applicable.

9. Data Management

It applies Electronic Data Capture(EDC) to complete the collection of trial data.EDC system has undergone strict testing, completely meet the requirements of “Quality Management Norm for Clinical Trial of Medical Devices”, “Data Management Work Technique Guideline for Clinical Trial”.Before the online of the system, it is necessary to carry out training and testing for the relevant application staff, to ensure that the system meet the requirement of the trial.After formal online, relevant staff would obtain the account and password.The account binds the roles and authority of the clients, and they should properly preserve the account information, and forbidden to divulge the account information to any others, or replace others in their performance of others rights.

9.1 Data Collection

EDC would directly upload the data from the clients terminals onto the server terminal through internet. The researcher is unnecessary to fill in the CRF in written form, they can direct record the source data into EDC system to accomplish the data collection. The researcher must be responsible for the quality of recorded data, to ensure the authenticity and integrity of data. EDC system provides the interface printing functions, and the researchers can print the electronic CRD information according to requirements.

9.2 Data Check up and Modification

EDC system provides two check up styles namely on line and off line. When the researcher record abnormal data, EDC system would issue real time warning to remind the researcher to check up the data; and the data manager would carry out logic check up for data preserved on the server, and release the wrong data in the form of artificial questioning through EDC. The researcher must answer the question released. And the monitor should routinely remind and assist the researcher to answer the questions, to ensure that each question is correctly processed. The system would record all the questions and the corresponding answer.

9.3 Database lockup

When all the data have been recorded and submitted, and all the questions have been answered, the system would enter soft lockup status. The statistician shall generate blind review report based on the current database. If the confirmed data would not be modified, it should be jointly signed of the lockup tables for the database by the sponsor, data manager, statistical responsible staff , and the data manager would complete the database lockup operation according to the table. Lockup database could not be modified again. If there actually exists errors influencing primary efficacy indices or safety indices, it is necessary for the sponsor, data manager, statistical responsible personnel to confirm the unlock for modification and sign the database unlock table, and the data manager shall modify the error data according to the unlock reasons and carry out quality control. After completion of error modification, it is necessary for the sponsor, data manager, statistical responsible staff to re-sign the lockup table for database.

X. Feasibility Analysis

10.1 Analysis of Success Possibility

Traditional ventricular septal defect occluder has been maturely used in interventional therapy of ventricular septal defect for more than ten years. It has been well accepted by patients for its small trauma and definite curative effect. In recent years, with the development of transthoracic occlusion, we have found that the stroke of transthoracic occlusion path is much shorter than that of percutaneous path, thus making it possible to reuse the absorbable occluder. In addition, polydioxanone, with good physical and mechanical strength, chemical stability,

biocompatibility and safety, is biodegradable, and is easy to process and form. Furthermore, because its molecular main chain also contains unique ether bonds, the polymer has both excellent toughness and good strength, and is completely superior to the traditional NiTi alloy material occluder with its degradable characteristics. However, for some patients who have a distrust of the application of the new specifications of the device, they can be communicated patiently on the national testing, the use of listed products and related clinical principles to try to obtain their understanding.

The design of this trial meets the clinical and statistical requirements, with the evaluation index clear and quantifiable, the evaluation time limit reasonable and predictable, and the endpoint evaluation method simple and executable. Therefore, the overall design of this clinical trial is practical and feasible.

10.2 Possibility analysis of failure

The main causes of operation failure or poor results may be related to the following factors: 1) proficiency in operation; and 2) inaccurate understanding of indications and contraindications.

XII. Quality Control of Clinical Trial

The Sponsor and the Investigator shall perform their respective duties. The main Investigator is responsible for designing the trial scheme and Case Report Form (CRF), which shall be used with the consent of the Co-investigators. A complete experimental organization shall be established, and the Principal Investigator shall be responsible for total quality control, confirmation and implementation of the responsibilities of personnel at all levels. Before the trial, the trial team will organize all participants to study the scheme. It is required that the Investigators participating in this trial are all qualified personnel trained by GCP, and strictly follow the clinical trial scheme and adopt standard operating procedures to ensure the quality control and quality assurance of the clinical trial. The original data must meet the requirements of GCP, and the laboratory inspection results must be correct and reliable. CRF and trial device shall be in the charge of a special person and kept in accordance with GCP requirements.

XII. Ethical Protection and Informed Consent in Clinical Trial

12.1 Ethical considerations

This clinical trial is implemented in accordance with the requirements of the *World Medical Congress Declaration of Helsinki*, the Medical Device Good Clinical Practice (GCP) and relevant national laws and regulations.

This scheme is jointly agreed and signed by the Investigator and the Sponsor, and will be implemented after being submitted to and approved by the Hospital Ethics Committee.

If there are problems in the actual implementation of the clinical trial for the scheme, the Principal Investigator shall propose to the Sponsor that the scheme shall be revised. After the negotiation and discussion of the participating research units, the team leader unit shall revise the scheme, submit it in writing to the Sponsor and each participating research unit for signature and approval, and then submit it to the Ethics Committee for approval before implementation.

12.2 Approval of trial scheme

The examination and approval of the clinical trial scheme shall be carried out by the Ethics Committee, and the clinical trial shall not be carried out until the final approval of ethics is obtained.

12.3 Informed consent process and informed consent form

After the research is fully clarified, each patient receiving the treatment (or legal authorized representative) shall sign the informed consent form and indicate the time.

The informed consent form must be signed before any activities or procedures related to this research are carried out.

The responsibility of Investigators is to ensure that the signing of informed consent is in accordance with the ethical principles of the *World Medical Congress Declaration of Helsinki*.

XIII. Provisions on Reporting Adverse Events and Device Defects

13.1 Adverse Events

Definition of Adverse Events

Adverse events refer to adverse medical events that occur after the subjects accept the trial products, but they are not necessarily related to the trial products.

Selective operation, combined operation and other expected diseases that have been clearly

identified in the pre-enrollment diagnosis are not considered as adverse events.

Determination of severity of adverse events

Mild: Not influence on daily activities;

Medium: Influence on daily activities;

Serious: Loss of daily activities.

Determination of relationship between adverse events and devices

Affirmatively relevant;

Probably relevant;

Possibly relevant;

Possibly irrelevant;

Irrelevant.

13.2 Countermeasures for adverse events

All adverse events occurring during the research must be recorded in the adverse event table. Investigators shall give targeted treatment and follow-up for adverse events until symptoms disappear or stabilize. Investigators shall make a preliminary judgment on adverse events, and the basic judgment is divided into intraoperative adverse events (any adverse event occurs within 24 hours after the operation), postoperative adverse events, and device-related or non-device-related adverse events.

13.3 Serious adverse events

Serious adverse events refers to events that occur during clinical trial, such as events causing hospitalization or prolonged hospitalization, disability, affecting work ability, endangering life or death, permanent injury or physical dysfunction, injury requiring treatment and intervention, fetal diseases, fetal death or congenital malformation, etc.

Selective operation, combined operation and other expected diseases that have been clearly identified in the pre-enrollment diagnosis are not considered as serious adverse events.

13.4 Forecast and measures of serious adverse events

The following complications may occur during surgical intervention of the occluder: arrhythmia, displacement or detachment of the occluder, rupture of chordae tendineae, tricuspid insufficiency, aortic regurgitation, residual shunt, hemolysis, and acute myocardial infarction.

1) Arrhythmia

There may be ventricular premature beat, ventricular tachycardia, bundle branch block and atrioventricular block during the operation, which usually disappear after changing the position and direction of guide wire, catheter and delivery sheath without special treatment. Ventricular fibrillation is rare, and electrical cardioversion shall be performed immediately once it occurs. Temporary cardiac pacemakers should be installed when the ventricular rate is too slow and the Adam-Stoke syndrome occurs. If no recovery is found after 3 weeks, permanent pacemakers shall be installed.

2) The occluder is displaced or falls off

It is related to small size of occluder and improper operation. If the occluder falls off, the bedside X-ray chest radiograph shall be performed immediately to confirm the location of the occluder. Meanwhile, it shall be extended upward along the original surgical incision. The occluder shall be removed and VSD repaired under extracorporeal circulation through the conventional median sternal incision.

3) Rupture of chordae tendineae

Surgical VSD occlusion is performed under the tricuspid valve without establishing a strongly supported sheath delivery track across the tricuspid valve. The incidence of tricuspid valve chordae tendineae ruptures is much lower than that of conventional percutaneous occlusion, because the latter can cause chordae tendineae ruptures if the guide wire passes through the chordae tendineae after the track is established. If rupture of chordae tendineae occurs, it shall be treated under extracorporeal circulation.

4) Tricuspid insufficiency

The incidence rate is 1.6%, which was related to defect location, operation mode and occluder size. The posterior septal VSD is closely related to tricuspid valve, which can cause obvious tricuspid regurgitation after the occluder is implanted. When releasing the occluder, the distal end of the sheath shall be pushed close to the occluder before rotating the push rod to prevent entanglement with the chordae tendineae. The edge of the occluder is too long, especially when

the occluder selected is too large, due to the small defect opening, the waist extension of the occluder is limited, and the edge is relatively long, or the disk of the occluder forms a spherical appearance, which occupies a larger space after release and affects tricuspid valve closure. Echocardiography monitoring shall be performed during the operation. If obvious tricuspid regurgitation is found, occlusion treatment shall be abandoned.

5) Aortic regurgitation

It is related to occluder and operation. For example, for VSD with poor edge, the edge of the occluder selected which is larger than the distance from VSD to aortic valve, and direct contact of the edge of the occluder with aortic valve will affect the closure of aortic valve.

The disc diameter of the left ventricle of the occluder is larger than 50% of the circumferential diameter of the outflow tract of the aortic valve, and after the occluder is placed, the outflow tract of the left ventricle can be deformed, resulting in incomplete closure of the aortic valve.

6) Residual shunt

Shunt through the occluder disappears in a short period of time after the polyester membrane mesh hole in the occluder is filled with blood components. Obvious residual shunt is found in patients treated by porous VSD occlusion because the occluder fails to completely cover the inlet and outlet. For porous VSD, the left of the occluder shall be ensured to completely cover the defect inlet, otherwise, the occlusion treatment shall be abandoned.

7) Hemolysis

It is related to the existence of residual shunt. High-speed blood flowing through the occluder can cause hemolysis, which is manifested as soy sauce urine, chills, anemia, renal insufficiency, etc. In this case, close observation shall be made. For patients with mild hemolysis, aspirin shall be stopped, hemostatic drugs shall be given intravenously, and sodium bicarbonate shall be given orally or intravenously. In case of shunt complicated with hemolysis caused by spring coil, another occluder or spring coil can also be placed. If hemoglobin < 70g/L, the occluder shall be removed surgically.

8) Acute myocardial infarction

There have been reports of acute extensive anterior myocardial infarction after operation in China, which may be caused by insufficient anticoagulant or heparin resistance during operation, resulting in thrombosis formed in catheter or occluder surface fall off to coronary artery. Such complications are very rare. In case of treatment difficulties, routine anticoagulation shall be performed during the operation. Generally, heparin anticoagulation shall be given according to 100U/kg, or heparin dosage shall be applied according to ACT trial

results. Close observation shall be made after the operation, such as abdominal pain or chest pain. Electrocardiogram should be checked in time, thrombolytic therapy can be carried out if it is found early.

13.5 Device defects

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

13.6 Reporting procedures and contact information

If a serious adverse event occurs in the clinical trial, the Investigator shall immediately take appropriate treatment measures for the subject, and report in writing to the management department for medical device clinical trial of the clinical trial institution to which it belongs, and notify the Sponsor in writing. The management department for medical device clinical trial shall, within 24 hours, report in writing to the Ethics Committee and the food and drug supervision and administration departments and health and family planning departments of the province, autonomous region and municipality where the clinical trial institution is located. For deaths, the clinical trial institution and Investigators shall provide all necessary information to the Ethics Committee and the Sponsor.

For serious adverse events and device defects that may lead to serious adverse events, the Sponsor shall report to the filed food and drug supervision and administration department and the health and family planning department at the same level within 5 working days after learning of the defects. Meanwhile, the Sponsor shall inform other clinical trial institutions and Investigators participating in the trial, and notify the Ethics Committee of the clinical trial institution in a timely manner through its management department for medical device clinical trial.

XIII. Revised Procedures for Clinical Trial Scheme

Before clinical verification, the verification plan is finalized and signed after revision upon discussion between the Investigators and the Sponsor, and is submitted to the Ethics Committee for approval before implementation.

If there are problems in the actual implementation of clinical verification for this scheme, the scheme needs to be revised, which shall be submitted to the Sponsor, and after negotiation and discussion between both parties, the Sponsor will revise the plan, submit it to all participating

research units for signature and approval, and then submit it to the Ethics Committee for approval before implementation.

If important new information related to products for verification is found, the informed consent form must be revised in writing and submitted to the Ethics Committee for approval before the consent of the subject is obtained again.

XV. Deviation of Clinical Trial Scheme

Deviations from the scheme include lack and inaccuracy of laboratory or follow-up data; the follow-up window does not conform to the scheme; the inclusion and exclusion criteria do not conform to the scheme, etc. All deviations shall be promptly notified to the Sponsor. In case of any deviation in order to protect the life and health of the subject, the Sponsor must be informed in a timely manner and approve such deviation.

For the subjects with laboratory examination deviation or clinical follow-up deviation, or the subjects selected for exclusion criteria deviation scheme, the data are entered into the corresponding analysis set according to the actual situation.

In case of disputes, a Clinical Events Committee (CEC) or a Data Monitoring Committee (DMC) can be established to decide and record the results through discussion.

XVII. Direct Access to Source Data, Files

The source file contains the data of clinical trial activities and is the first-hand data recorded by the trial data. Any observation and inspection results in the trial shall be recorded in the source file in a timely, accurate, complete, standardized and true manner.

Source files: informed consent form, subject identification code form, subject screening form and inclusion form, subject's medical documents, trial device usage record form and serious adverse reaction report form.

Source data: subject name, date of birth, gender, trial identification code, scheme number, trial device name, trial screening or entry start date, trial device use date, specification number, signature of Investigator, serious adverse event and its treatment.

During the experiment, the monitors, inspectors, Ethics Committee and relevant drug supervision and administration departments related to the experiment shall be allowed to access

to these documents in order to verify the trial procedures or trial data, and shall abide by the confidentiality provisions.

XVIII. Finance and Insurance

The Sponsor shall pay the relevant fees according to the contract before the start of the trial to ensure the smooth progress of the trial, and shall not cause the subjects to pay extra fees in any ways; Shanghai Shape Memory Alloy Co., Ltd purchased the clinical trial liability insurance from Taiping Property Insurance Co., Ltd. For the subjects. If the subject suffers injury or death related to clinical trial, Shanghai Shape Memory Alloy Co., Ltd shall bear the cost of treatment and corresponding economic compensation, except for the damage caused by the fault of medical institutions and their medical personnel in the diagnosis and treatment activities.

XVIII. Trial Summary Report

The clinical trial report shall be consistent with the trial scheme, shall be signed and dated by the lead unit investigator, and shall be submitted to the Sponsor after being reviewed, stamped and dated by the management department of the medical device clinical trial institution, and the authenticity and confidentiality of clinical data shall be ensured.

XIX. Confidentiality Principle

This agreement, the contents of this clinical trial and all attached data are confidential and belong to the Sponsor only, for which the Investigator shall be responsible for confidentiality. Such information, including the patent application, manufacturing process and unpublished data provided by the Sponsor to Investigators for use, etc., shall not be disclosed to any third party except with the consent of the Sponsor, and the confidentiality obligation shall remain valid after the termination or end of this trial.

XX. Agreement on Publication of Trial Results

Investigators have the right to write papers, reports, etc. on the experiment, but Investigators shall notify the Sponsor in writing before publication, and shall not violate the confidentiality obligations agreed in this scheme.

XXI. Responsibilities of Various Parties

21.1 Responsibilities of Institutions and Investigators

Clinical trial institutions and Investigators shall reach an agreement with the Sponsor on matters related to the clinical trial. Before starting clinical trial, Investigators shall cooperate with the Sponsor to apply to the Ethics Committee and submit relevant documents according to regulations.

Investigators shall organize relevant personnel to get familiar with the principle, application scope, product performance, operation method, installation requirements and technical indexes of the medical devices for testing according to the latest Investigator's Brochure and other data provided by the Sponsor, understand the preclinical research data and safety of the medical devices for testing, and master the prevention and emergency treatment methods of risks that may arise from the clinical trial recommended by the Sponsor.

21.2 Responsibilities of the Sponsor

The Sponsor is responsible for initiating, applying, organizing and supervising the clinical trial, and is responsible for the authenticity and reliability of clinical trial.

The Sponsor is responsible for organizing the formulation and revision of Investigator's Brochure, clinical trial scheme, informed consent form, case report form, relevant standard operating procedures and other relevant documents.

The Sponsor shall select institutions and Investigators from the medical device clinical trial institutions approved by the state according to the characteristics of the medical device for testing. Before signing the clinical trial agreement with the clinical trial institution, the Sponsor shall provide the latest Investigator's Brochure and other relevant documents to the clinical trial institutions and Investigators for their review and decision on whether they can undertake the clinical trial.

In organizing the formulation of the clinical trial scheme, the sponsor shall not exaggerate on the mechanism and efficacy of medical devices used in the trial.

In the process of the clinical trial, when the Sponsor obtains new important information, he shall revise the Investigator's Brochure and related documents in time and submit them to the

Ethics Committee for review through the Investigators, and submit them to all Investigators after obtaining the approval.

XXI. References

Expert Consensus on Interventional Diagnosis and Treatment of Common Cardiovascular Diseases by Surgical Approach, by Hu Shengshou, Pan Xiangbin, and Chang Qian. Expert Consensus on Interventional Diagnosis and Treatment of Common Cardiovascular Diseases by Surgical Approach [J]. Chinese Journal of Circulation, 2017, 2: 001.

Animal Experimental Study on Safety and Effectiveness of Degradable Ventricular Septal Defect Occluder, by Chen Yidan, Pan Yifeng, Zhao Tianli. Animal Experimental Study on Safety and Effectiveness of Degradable Ventricular Septal Defect Occluder [J]. China Journal of Modern Medicine, 2017, 27(13): 44-49.

Animal experimental study of the fully biodegradable atrial septal defect (ASD) occluder Zhu Y, Huang X, Cao J, et al. Animal experimental study of the fully biodegradable atrial septal defect (ASD) occluder[J]. BioMed Research International, 2012, 2012.

Guiding Principles for Design of Clinical Trial of Medical Devices - Circular of the General Administration on Issuing Guiding Principles for Design of Clinical Trial of Medical Devices (No.6, 2018)

Code for Quality Management of Clinical Trial of Medical Devices -Order No.25 of National Health and Family Planning Commission of PRC, China Food and Drug Administration

XXII. Clinical Trial Institutions and Investigators and Sponsors Sign the Trial Scheme

Declaration of the investigator:

I agree to:

1. Carry out this clinical trial in strict accordance with the current laws and regulations of Declaration of Helsinki and China and the requirements of this trial scheme.

2. Record all required data in Case Report Form (CRF) accurately and complete clinical trial summary report on time.

3. The trial products are only used for this clinical trial. The reception and use of the trial products shall be recorded completely and accurately during the clinical trial, and the records shall be kept.

4. Allow the monitor and regulatory authorities authorized or dispatched by the Sponsor to supervise and inspect the clinical trial.

5. Strictly implement the terms of the clinical trial contract and relevant agreements signed by both parties.

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

Sponsor's Comments:

Signature (Seal)

Date

Investigators' Comments:

Signature

Date

Perspective, multiple-centered, randomized control method evaluation
The safety and efficacy for clinical application of completely degradable occlusion system for ventricular septal defect
Version number : XZKJ-1801-V1.0

Comments of Medical Device Clinical Trial Institutions:

Signature (Seal)

Date