Cover Page

Protocol Title	A multicenter, open label, prospective, randomized study of the MYNXGRIP Vascular Closure Device in subjects with diagnostic or interventional endovascular procedures (PANDA Study)
NCT Number	NCT03923387
Version Number and Date of Protocol	V2.0, 27-Dec-2019

Clinical Study Protocol of Medical Devices

Clinical Study Protocol of MynxGrip

Protocol number: P17-0005

Protocol Title: A MULTICENTER, OPEN LABEL, PROSPECTIVE, RANDOMIZED STUDY OF THE MYNXGRIP VASCULAR CLOSURE DEVICE IN SUBJECTS WITH DIAGNOSTIC OR INTERVENTIONAL ENDOVASCULAR PROCEDURES (PANDA study)

Name of the investigational medical device: MynxGrip

Model/specification: MX5021, MX6721

Category of the investigational medical device:

Class III medical device requiring clinical trial approval **Yes** □ **No** ☑

Predicate product approved in China **Yes** ☑ **No** □

Version number and date of the protocol: V2.0 (Dec 27, 2019)

Study site: Beijing Tian Tan Hospital, Capital Medical University

Investigator: Professor Miao Zhongrong

Statistical analysis: Kuntuo Medical Research & Development (Beijing) Co., Ltd.

Sponsor: Access Closure, Inc., a Cardinal Health company

Agent: Cordis (Shanghai) Medical Device Co. Limited

Completion Instructions:

1. **For multi-center clinical trials, the "Study site" on the cover of the protocol should contain only the leading site and the other sites should be listed in the text.**
2. **For multi-center clinical trials, the "Investigator" on the cover of the protocol should contain only the coordinating investigator.**

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Abbreviations

AE	Adverse event
CABG	Coronary artery bypass grafting
CRA	Clinical research associate
CRO	Contract Research Organization
CFDA	China Food and Drug Administration
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full analysis set
GCP	Good Clinical Practice for Medical Devices
ICF	Informed consent form
INR	International normalized ratio
PPS	Per protocol set
SAE	Serious adverse event
SS	Safety set

1 Sponsor information

1.1 Name of sponsor

Access Closure, Inc., a Cardinal Health company

1.2 Address of sponsor

5452 Betsy Ross Drive

Santa Clara

California

95054

USA

1.3 Contact information of sponsor

Zip code: 95054
Telephone: +1 408-273-3700
Fax: +1 408-955-0457

1.4 Related qualification documents of sponsor

Quality management system certificate

1.5 Agent information

Name of agent: Cordis (Shanghai) Medical Device Co. Limited
Address of agent: Room 506, No. 222, Meiyue Road, Pilot Free Trade Zone, Shanghai, China
Contact information of agent: Wen Xuan 13501164197
Related qualification documents of agent: Business license

2 List of study sites and investigators for the multicenter clinical trial

Code of study site	Name of study site	Investigator	Title	Contact information
01	Beijing Tian Tan Hospital, Capital Medical University	Miao Zhongrong	Chief Physician	13601243293
02	Xuanwu Hospital, Capital Medical University	Jiao Liqun	Chief Physician	13911224991
03	Department of Vascular Surgery, West China Hospital, Sichuan University	Zhao Jichun	Chief Physician	18980601368

04	Department of Cardiology, West China Hospital, Sichuan University	Wang Hua	Associate Chief Physician	18980602038
05	Nanjing First Hospital	Gu Jianping	Chief Physician	13505171786
06	Changhai Hospital of Shanghai	Liu Jianmin	Chief Physician	13901780638

3 Objective and contents of the clinical trial

3.1 Objective

This study is to evaluate the safety and effectiveness of MynxGrip, a vascular closure device indicated for use to seal femoral arterial access sites while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular procedures utilizing a 5F, 6F or 7F procedural sheath.

3.2 Contents

This study is designed as a prospective, multi-center, randomized, open-label, parallel-controlled study, in which superiority trial will be conducted to demonstrate the effectiveness, and non-inferiority trial will be conducted to demonstrate the safety, of the MynxGrip compared with the control group. MynxGrip will be used for the subjects in the test group who have undergone diagnostic or interventional endovascular procedures utilizing a 5F, 6F or 7F procedural sheath, to evaluate the safety and effectiveness of MynxGrip in hemostasis of common femoral artery puncture site, compared with manual compression hemostasis used for those in the control group undergoing the same procedures. A 30-day follow-up will be conducted to the eligible subjects of both test group and control group after receiving hemostasis treatment, wherein the time to achieve hemostasis, time to ambulation, procedure success rate, device success rate, length of stay (for patients receiving diagnostic procedure), incidence of major and minor complications, adverse events, severe adverse events, etc., will be recorded and evaluated.

4 Background information of clinical trial

Intravascular catheterization is a minimally invasive medical technology using interventional catheter to diagnose or treat the deep-seated intravascular lesions (in coronary artery, brain, liver and kidney, etc.). It now plays a significant role in angiography, angioplasty, removal of thrombus or foreign bodies in the blood vessel, cancer chemotherapy, treatment of vascular malformation, etc. As the femoral artery is large, straight, stable and easy to be palpated and punctured, it is often used as access in the intravascular interventional diagnosis and treatment.

Manual compression hemostasis is the most traditional and most commonly used method to achieve hemostasis of femoral artery. It is economical and is a relatively reliable backup method when other hemostatic methods fail. It is also a time-consuming work with disadvantages such as prolonged time to achieve hemostasis and bed rest, and more likely to cause complications in obese patients or if the puncture sites are too high or too low So, there are a variety of ways as a supplementary and alternative to the traditional manual compression, e.g. supplementary compression with dressing, mechanic compression, vascular closure device, etc. Of which the vascular closure device has advantages of shorter time to achieve hemostasis, more comfort for the patients, etc.

Vascular closure device, through different principles/techniques, occludes the artery puncture site to achieve hemostasis. According to the principles, vascular closure devices can be divided into suture-based and non-suture-based. Perclose is the widely used suture-based closure device available in the market; non-suture-based closure devices available in China include:Starclose, a nitinol clip-based closure device; EXOseal and Angio-Seal, bioabsorbable plug-based and collagen-plug-based closure devices for extravascular hemostasis; Co-Close, a Chinses brand artery closure device using alloyed occluder for hemostasis, etc. [1]The investigational medical device - MynxGrip is a non-suture-based vascular closure device for extravascular hemostasis.

The investigational medical device - MynxGrip and its predecessor (Mynx) have been marketed overseas for many years and are widely used. Studies on their safety and effectiveness have been reported in some literature.

In the study, Safety and efficacy of percutaneous femoral artery access followed by Mynx closure in cerebral neurovascular procedures: a single center analysis, conducted by Grandhi R, et al. from 2009-2010 [2],a total of 766 subjects underwent 937 neurovascular procedures in a ten months period. The device success rate was 92% and the complication rate was 2.45%, with older age, lower BMI, higher number of antithrombotic medicines used, higher international normalized ratio and lower platelet count conferring an increased risk of complication.

In the study, Active (AngioSeal) Versus Passive (Mynx) Anchoring Vascular Closure Devices Following Percutaneous Coronary Intervention: A Safety and Efficacy Comparative Analysis, conducted by Baker N C, et al., [3], a total of 4,074 subjects were included; the study concluded that AngioSeal and Mynx were equally safe and efficacious VCDs following PCI.

In the study, Single-center comparison of the efficacy and complications of arterial vascular closure devices in interventional radiology, conducted by Elmasri M A et al.[4]

retrospective analysis of 907 consecutive arterial procedures in interventional radiology was performed. Five VCDs were used: AngioSeal, FISH, Mynx, Perclose and Starclose; subjects who underwent manual compression without use of VCDs were studied as the control group. The results showed that the complete hemostasis success rate (also known as technical success rate) was 93.5%, 53.6%, 89.3%, 73.7% and 76.5% for VCDs, respectively, while 91.5% for manual compression; the total incidence rate of major complications was 1.5%. There was significant difference in effectiveness between various hemostasis methods, while no difference in safety. It also pointed out that the reason for lower technical success rate in Mynx group was probably because that the investigators were not familiar with the operation of Mynx compared to other VCDs. Meanwhile higher ratio of subjects with cirrhosis and lower platelet count in Mynx group might be another factor. Overall, there was no significant correlation of unsuccessful failure or the complication probability with the patients' demographic data and laboratory indicators.

Fargen K M et al.[5] carried out a prospective, randomized, single-blind trial comparing the patient comfort following vessel closure using Mynx and Angio-Seal. 64 subjects who received the diagnostic cerebral angiography via femoral artery puncture were enrolled. The results showed that the pain at closure and pain increase from baseline to closure were significantly higher in the AngioSeal group than in the Mynx group. No adverse events were found in both groups. It showed that Mynx provides less pain than AngioSeal following vessel closure.

In the study conducted by Hutchings D, et al. [6], a retrospective analysis of 432 patients who received vessel closure using Mynx following coronary angiography was performed. A 100% successful deployment using Mynx device was achieved, with 3.2% requiring conversion to manual compression 99.5% of patients were discharged on the same day. 0.7% of patients had confirmed hematoma >5cm. The hematoma was associated with hypertension. Postangiography use of the Mynx closure device was highly successful, safe, and well-tolerated with a low complication rate, allowing safe same-day discharge.

A study conducted by Jr P M, Blachut A M et al.[7] evaluated the safety and effectiveness of MynxGrip in peripheral interventions with anterograde access. 66 patients were included; all patients were discharged on the same day of procedure. No major complications were observed. The minor complication rate was 7.6%. In 1 patient, a second VCD was deployed after device failure. No patients required hospitalization. No hematoma >6cm was observed. MynxGrip was safe and effective in sealing access sites after anterograde femoral artery puncture..

In a study conducted by Scott M C, et al. [8], a retrospective analysis of 894 patients undergoing arterial endovascular procedures with percutaneous access(including the

anterograde and retrograde puncture) was performed. Compared with manual compression, the use of MynxGrip, Angioseal and Perclose had a lower rate of bleeding complication, device failure and operative repair. Bleeding was related to the age, interventional procedures and end stage renal disease. MynxGrip, Angioseal and Perclose had similar rates of complications. Uses of these devices were a safe option for groin vessel closure.

In conclusion, many clinical literature have reported the clinical use, advantages and characteristics of - MynxGrip,, demonstrating that MynxGrip is safe and effective in sealing access sites of femoral artery puncture following a diagnostic or interventional endovascular procedure.

5 Characteristics, structural composition, operation principle, mechanism of action and study population

5.1 Product characteristics

The vascular closure device (MynxGrip) is designed to achieve femoral artery hemostasis via delivery of an extravascular, water-soluble synthetic sealant using a balloon catheter in conjunction with a standard procedural sheath. The sealant is made of a polyethylene glycol (PEG) material which expands upon contact with subcutaneous fluids to seal the arteriotomy. The sealant is resorbed by the body within 30 days.

The vascular closure device MynxGrip is supplied with a 10 ml locking syringe used for balloon inflation and deflation. There are no components manufactured from latex rubber. The vascular closure device MynxGrip 5F device has a gray shuttle. The vascular closure device MynxGrip 6F/7F device has a green shuttle.

5.2 Structural composition, operation principle and mechanism of action

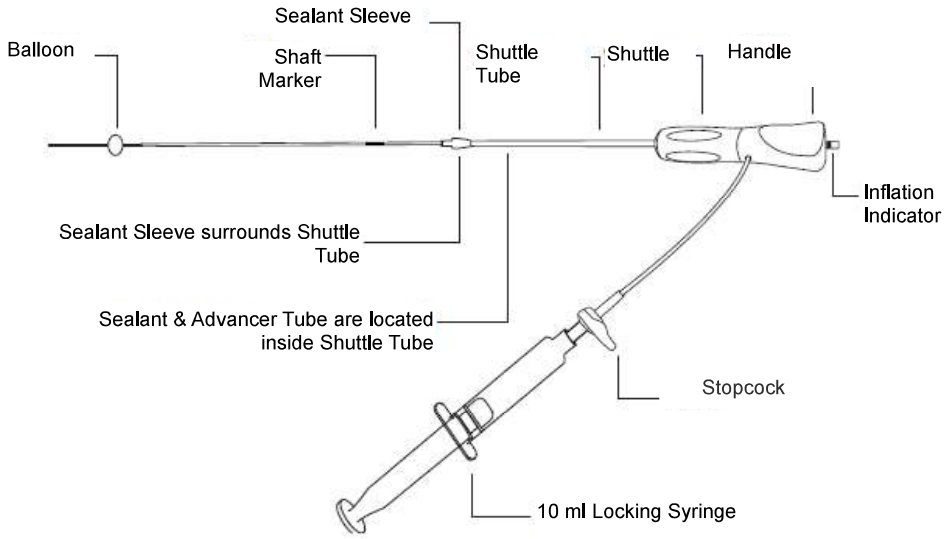
5.2.1 Structural composition

The MynxGrip includes (Figure 1):

(1) Balloon catheter with integrated sealant

(1) 10 ml locking syringe

Figure 1: MynxGrip Device Balloon Catheter



The MynxGrip 5F device has a gray shuttle. The MynxGrip 6F/7F device has a green shuttle.

5.2.2 Operation principle/mechanism of action

The MynxGrip is designed to achieve femoral artery hemostasis via delivery of an extravascular, water-soluble synthetic sealant using a balloon catheter in conjunction with a standard procedural sheath. The sealant is made of a polyethylene glycol (PEG) material which expands upon contact with subcutaneous fluids to seal the arteriotomy. The sealant is resorbed by the body within 30 days.

5.2.3 Trial scope and training

The vascular closure device MynxGrip models MX5021, MX6721 are used in this trial.

Investigators/operators will be trained before using the vascular closure device MynxGrip. Training will include teaching demo for the device and the hemostasis process, and hands-on training on a bench model. Training will be provided by representatives or affiliates of the Sponsor (Access Closure, Inc., a Cardinal Health company).

The first 60 subjects enrolled in this trial will enter the trial group directly, using the experimental medical device for intervention; the investigator/operator will be able to receive guidance from the sponsor's technical staff to control the investigator's Operational bias.

6 Product's indications, contraindications and precautions

6.1 Indications

MynxGrip is indicated for use to seal femoral arterial access sites while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular procedures utilizing a 5F, 6F or 7F procedural sheath.

6.2 Contraindications

There are no known contraindications for the investigational medical device.

6.3 Precautions

MynxGrip should only be used by a trained licensed physician or healthcare professional.

MynxGrip should not be used in patients with a known allergy to PEG.

Warnings:

Do not use if components or packaging appear to be damaged or defective or if any portion of the packaging has been previously opened.

DO NOT REUSE OR RESTERILIZE. The vascular closure device MynxGrip is for single use only. The balloon catheter is loaded with a single Hydrogel sealant. Reuse of the device would result in no delivery of Hydrogel sealant.

Do not use the vascular closure device MynxGrip if the puncture site is located above the most inferior border of the inferior epigastric artery (IEA) (for arterial application) and/or above the inguinal ligament based upon osseus landmarks, since such a puncture site may result in a retroperitoneal hematoma/bleed. Perform a femoral angiogram to verify the location of the puncture site.

Do not use the vascular closure device MynxGrip if the puncture is through the posterior wall or if there are multiple punctures, as such punctures may result in a retroperitoneal hematoma/ bleed.

7 Overall design

7.1 Study design

7.1.1 Study objective

To evaluate the safety and effectiveness of the vascular closure device (MynxGrip) in sealing femoral arterial access sites in patients who have undergone diagnostic or interventional endovascular procedures, including:

Effectiveness: to evaluate whether MynxGrip group is superior to the control group in time to hemostasis, compare whether there are differences in the time to ambulation, procedure success rate and length of stay (for patients receiving a diagnostic procedure) between the two groups, and evaluate the device success rate of the test group.

Safety: to evaluate whether the major complication rate of MynxGrip group is not inferior to the control group, and compare whether there are differences in minor complication rate, adverse events and severe adverse events between the two groups.

7.1.2 Study method selection and its rationale

This clinical trial is a clinical verification for the registration of medical device, so it is required to follow the requirements of related regulations of Administrative Measures for Medical Device Registration (2014), Good Clinical Practice for Medical Devices (2016) and Guidelines for Clinical Trial Design of Medical Device (2018) which are issued by the China Food and Drug Administration (CFDA). This study is designed as a prospective, multi-center, randomized, open-label, parallel controlled study.

7.1.2.1 Rationale for selection of control group

Investigate the effectiveness and safety of the investigational medical device, and evaluate its clinical application value;compare the similarities and differences in sealing femoral artery puncture sites between the investigational medical device and the existing hemostatic methods, so as to provide guidelines for clinical application. Manual compression is used as the control group. Rationale is as follows:

(1) So far, there are no vascular closure devices having the same structure composition as MynxGrip imported or marketed in China.

(2) Manual compression hemostasis is the most traditional and most commonly used method to achieve hemostasis of femoral artery. This method is easy to operate, with low cost and good hemostatic effect. Its effectiveness and safety have been widely recognized in clinical use. Many clinical trials and literature both at home and abroad have demonstrated the disadvantages of manual compression, compared with vascular closure devices, including being labor

and time-consuming in achieving hemostasis, prolonged time to ambulation after surgery and discomfort.

(3) Other hemostatic methods (mechanical compression, hemostatic materials and vascular closure devices, etc.) have also been used for femoral artery puncture site hemostasis, but none is widely recognized as the “gold standard” in clinical use, and manual compression is always backup method when the other methods fail to achieve hemostasis, and therefore, these methods and the traditional manual compression have their own strengths and weaknesses.

With regard to primary effectiveness indicators, superiority trial will be conducted to demonstrate whether the time to hemostasis in the test group is superior to the control group, so as to facilitate operation for medical personnel and improve the patient's comfort. Meanwihle, the safety will be evaluated by non-inferiority trial to demonstrate whether the investigational medical device is not inferior to the control group.

7.1.2.2 Rationale for selection of the study population

According to the indications for use in the IFU of the investigational medical device “indicated for use to seal femoral arterial and femoral venous access sites while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular procedures utilizing a 5F, 6F or 7F procedural sheath”, the study population selected for this clinical study is the “subjects who plan to receive the diagnostic or interventional endovascular procedures via percutaneous common femoral artery puncture”. The study population meets the scope of application of the investigational medical device and control methods.

This study makes the references to the nationally and internationally already existed literature reports of clinical study and the clinical trial design. Some factors that could increase the safety risk of subjects are excluded, ensuring the safety of the subjects to the maximum from the point of ethics.

7.1.2.3 Rationale for selection of the endpoints

The primary effectiveness endpoint of this clinical study is the: Time to Hemostasis. The time to hemostasis is the intuitionistic index to evaluate the hemostatic efficiency at common femoral artery puncture site, also the superiority of the investigational medical device. The primary effectiveness indicators are selected based on the trial objective; they are easy to be quantized and more recognized in related research fields. Other effectiveness indicators include: time to ambulation, procedure success rate, device success rate, length of stay (for patients receiving diagnostic procedures), which reflects the overall hemostatic effect of the device, operational feasibility and the patients’ quality of life after hemostasis, so as to evaluate the effectiveness of the investigational medical device from different aspects.

The primary safety endpoint of this clinical study is the: major complication rate. Other safety indicators included the minor complication rate, adverse events and severe adverse events, which are used to evaluate the safety of the investigational medical device in common femoral artery puncture site hemostasis.

7.1.2.4 Rationale for selection study duration

The visit schedule and rationale for selection:

(1) **Visit 1:** Screening period (Day-7 - 0h); the patients sign the informed consent form. In accordance with the inclusion criteria and preoperative exclusion criteria, the patients will receive the relevant examinations to confirm whether they are eligible.

(2) **Visit 2:** Interventional diagnosis and treatment and hemostasis (Day 1); ineligible subjects are excluded, and perform hemostasis using investigational medical device/control methods for the common femoral artery puncture sites in the patients undergoing interventional diagnosis and treatment. The time to hemostasis, procedure success rate and device success rate are recorded. The occurrence of complications and adverse events are continuously observed.

(3) **Visit 3:** Off-bed visit (Day 1-2); the patient can get out of the bed after surgery. The time to ambulation is recorded. The patients are continuously observed for occurrence of complications and adverse events.

(4) **Visit 4:** Discharge visit (on the same day of discharge); after being assessed by the investigators, the patients recover well and could be discharged. The vital signs are evaluated and the occurrence of complications and adverse events are observed.

(5) **Visit 5:** Post-discharge follow-up (Day 30±7); the polyethylene glycol sealant applied by MynxGrip will have been completely resorbed by the subject at this point. The vital signs are evaluated. The blood routine examination is conducted. The adverse events and complications occurred in post-discharge period are collected.

7.1.3 Measures to reduce and avoid bias

Multi-center: the samples from multi-center are more representative than those from single center, the latter may lead to deviation of test results due to its systematic errors.

Randomization: the randomization allows the patients to be given equal opportunity to be assigned to the test group or control group, independently of subjective views of investigators and/or subjects, so that the various influencing factors tend to be distributed in a similar way, avoiding the issues of selection bias and information bias. In this trial, the patients are randomized into groups, reducing the trial bias caused by

sampling error. After the verification of inclusion criteria and exclusion criteria, the investigators randomly assign the devices into the test group and control group for treatment according to the time in which the subjects receive the interventional diagnosis and treatment via common femoral artery. The randomization number table is generated by the biological statistics personnel using PLAN process of SAS before the first subject is included in the study.

Parallel controlled: this is a parallel controlled trial, in which treatment is conducted simultaneously for both the test group and the control group, so that potential differences influencing the outcome measures between both groups can be minimized.

Training of investigators: Prior to the clinical trial, the Clinical Research Associate, coordinating with the persons in charge of the study sites, will train the investigators on the study protocol, making sure they are familiar with the use of investigational medical device, and implement patient enrollment strictly in accordance with the inclusion criteria and exclusion criteria, conduct relevant examinations according to the protocol requirements, also master all new device related information found during the clinical trial, thus to minimize the interferential factors.

Monitoring of clinical trial: The monitoring plan is established. The Clinical Research Associate is selected and appointed by the sponsor to conduct a regular on-site monitoring visit of trial hospital, making sure that all contents in the trial protocol are strictly followed. The raw materials are inspected to ensure consistent contents with the electronic case report form (eCRF).

Audit of clinical trial: the audit on the study conducted, independently by the audit department of the Contract Research Organization (CRO) and the sponsor, with regular on-site audit and spot check on the study sites, so as to make sure that the Clinical Research Associate monitors the study according to the monitoring schedule, all procedures in the trial protocol are strictly followed, and contents in the eCRF are consistent with that in the raw materials..

7.1.4 Investigational medical device and control device

7.1.4.1 Investigational product and control product

(1) Test group:
Product name: MynxGrip
Specification/model: MX5021, MX6721
Manufacturer: Access Closure, Inc, a Cardinal Health company
(2) Control group: manual compression

7.1.4.2 Management of medical device

(1) The investigational medical devices are uniformly labeled and numbered, indicating for clinical trial use only. There should be the special person to check and perform process documentation.

(2) The investigational medical device should be sent by a special person appointed by the sponsor directly to each study site. The study site shall handle the complete transfer procedures of investigational medical device with the sponsor.

(3) Each study site shall set up a special location for storing the investigational medical devices below 25 ℃.

(4) Each study site shall establish a strict management system of investigational medical device. The investigational medical device should be managed by the special person other than the investigators. A dedicated “Record Form of the Use of Medical Device for Clinical Trial” should be established. The administrator shall provide the investigational medical devices, in numeric sequence, to the subjects based the chronological order of their enrollment. The subject names, the date on which the device is provided, and the serial numbers of the devices are recorded with signature. During the trial, the investigators shall faithfully record the number of used and unused devices.. At the end of the trial, the unused investigational medical device should be returned to the sponsor.

7.1.5 Selection of subjects

7.1.5.1 Inclusion criteria

Subjects are included in this clinical study only if they meet all of the following criteria:

1) Patients ≥ 18 years of age;
2) Patients who are able and willing to sign the informed consent form;
3) Patients who agree to follow all study visits and procedures;
4) Patients who plan to receive the diagnostic or interventional endovascular procedures via percutaneous common femoral artery puncture;
5) Patients who are able to walk, as judged by the investigators.

7.1.5.2 Exclusion criteria

Subjects are excluded from this study if any of the following criteria is met:

Preoperative exclusion criteria

1) Patients are proved to have clinically significant peripheral vascular disease according to any of the following situations:

a. Patients showing severe claudication with bilateral after walking less than 200 meters,
b. No palpable pulse on the patients' the ipsilateral common femoral artery,
c. Patients having received surgical procedures involving the ipsilateral common femoral artery
d. Patients having received percutaneous transluminal angioplasty (PTA), stent placement, or vascular graft in the ipsilateral common femoral artery;

2) Patients with morbid obesity (BMI > 40 kg/m^2);
3) Patients with a myocardial infarction (MI) with acute elevated ST segment ≤72 hours prior to procedure;
4) Patients with the prior procedure in the ipsilateral common femoral artery ≤30 days;
5) Patients having received ipsilateral vascular closure device;
6) Patients with bleeding disorders such as thrombocytopenia (platelet count < 100,000/ mm^3), hemophilia, von Willebrand disease or severe anemia (Hgb < 10 g/dL, Hct < 30%);
7) Patients with documented INR > 1.5 or patients currently receiving glycoprotein IIb/IIIa platelet inhibitors;
8) Patients with symptoms of local infection or inflammation in the groin;
9) Patients who are participating in any other clinical studies on drugs or medical devices at the same time;
10) Patients who are pregnant or in lactation;
11) Patients with known allergy to contrast medium;
12) Patients with known allergy to polyethylene glycol;
13) Patients with treated but still uncontrolled hypertension (systolic pressure>180 mmHg or diastolic pressure>110 mmHg);
14) Patients with known autoimmune diseases;
15) Patients who are receiving long-term corticosteroid therapy;
16) Patients with expected life of less than 30 days;
17) Patients with unilateral or bilateral lower-extremity amputation;
18) Patients who can't walk 6 meters (20 steps) without a support for any reason;
19) Patients requiring prolonged length of stay [For example, the patient will receive the coronary artery bypass grafting (CABG) or the patient plans to receive the CABG ≤30 days after the surgery];
20) Patients with mental disorders and cognitive impairment
21) Patients have participated into this study before;

Intra-operative exclusion criteria

22) Patients with treated but still uncontrolled hypertension (systolic pressure>180 mmHg or diastolic pressure>110 mmHg);
23) Patients implanted with a balloon pump inside the aorta;
24) Patients whose common femoral artery is too thin (<5 mm in diameter);
25) Patients with obviously fibrotic, calcified, or >50% stenotic femoral artery;
26) Patients having received puncture at other lower extremity artery than the common femoral artery;
27) Patients having received antegrade puncture;
28) Patients having received lower extremity arterial puncture at a number of different sites or who are suspected to have received posterior femoral arterial wall puncture;
29) Patients implanted with ipsilateral venous sheath;
30) Surgical findings or complications which the investigators consider may interfere with the patients' participation into the study (For example, the sheath deployment is difficult due to the scar, tortuous vessels, or use of the sheath with the other sizes than 5 Fr, 6 Fr or 7 Fr, or the sheath with the total length of >15.7 cm);
31) Patients with preexisting hematoma, intraluminal thrombus, pseudoaneurysm, AV Fistula or any type of dissection;
32) Patients requiring prolonged length of stay [For example, the patient will receive the coronary artery bypass grafting (CABG) or the patient plans to receive the CABG ≤30 days after the surgery];
33) Patients who are included in another drug or medical device study.

7.1.5.3 Criteria and procedures for withdrawal/termination of study

(1) Drop-out criteria

Definition: it refers the situation in which a subject can't continue his/her participation in a study till the last follow-up as required by the protocol for any reason.

Management of drop-out cases: all drop-out cases shall be recorded in the CRF with study conclusions and causes. The investigators shall ensure the subjects' compliance as much as possible by frequently contacting with them, asking subject the reason for drop out, recording complications and adverse events, so as to make the evaluation items as complete as possible.

(2) Withdrawal criteria

It refers to the situation in which a subject's participation in this study is prematurely terminated. To terminate the subject's participation is to protect the subject's rights, ensure the quality of the trial, and avoid unnecessary economic losses. The

investigator may terminate a subjects participation in the study, in case of any of the following situations:

- Presence of serious safety problems;
- Subject's condition deteriorated;
- Other management-related reasons.

The subject has the right to withdraw from the study at any time for any reason. If the subject decides to withdraw from the study, the investigator shall ascertain the reason for the withdrawal, for example: adverse events, failure of corrective treatments, the investigator's decision or other reasons. The reasons should be recorded in the eCRF.

The investigator has the right to terminate the subject's participation in the study in case of the above-mentioned circumstances: the investigator will have to make a detailed evaluation for the subject withdrawn from the study, take active treatment measures, and record this process in the original record in details. If the withdrawal is due to adverse events, abnormal laboratory testing values or treatment failure, the investigator shall also make the corresponding evaluation and treatment and record this process in the original record in details. The investigator may also terminate the subject's participation in the study at any time depending on the medical analysis.

(3) Criteria for termination of study

The termination of study refers to the situation in which the trial is terminated before completing evaluation of all the subjects as planned. After the termination of trial, no new subjects will be included. The included subjects, who have not finished the study, will receive treatment and follow-up according to the negotiation result of the sponsor and the investigators.

- If the investigational medical device is found to have no clinical value during the study, the trial should be terminated;
- The trial shall be terminated if significant mistakes in the study protocol which will lead to difficulty in evaluating the safety and effectiveness of the investigational medical device is found during the trial;
- Presence of serious deviation during the study, which will lead to difficulty in evaluating the safety and effectiveness of the investigational medical device;
- Sponsor's request for termination (because of the cost, management, etc.);
- Regulatory Authority's order for termination of trial for some reason;
- Ethics committee's request for termination from the prospect of protecting the subject's rights.

7.1.5.4 Time of enrollment

Prior to the screening, the ICF signed by the subjects shall be obtained; as judged by the investigator, subjects who meet all the inclusion criteria and do meet any of the exclusion criteria (including the preoperative and intraoperative exclusion criteria), will be included in this study; this time point is regarded as the time in which this subject is included in the study.

7.1.5.5 Expected overall duration of clinical trial and reasons for determination

Expected overall duration:

The overall duration of clinical trial is expected to be 20 months, including the processes of protocol signing by all study sites, ethical committee review meeting and rectification and filing after the meeting, trial initiation, enrollment and follow-up, collection and statistical analysis of study data, preparation of final report, etc.

Reason: The overall duration of this trial is predicted based on the number of the investigational products used for the outpatients in each hospital to ensure adequate source of cases for the investigational medical devices, the patient follow-up schedule and the process systems of the hospitals.

7.1.5.6 Expected duration of participation of each subject

The duration of subject participation is defined as a period from the time that the subject agrees to be included in the study and starts to participate into the trial to the end time of the final follow-up. The expected duration of subject participation is estimated to be about 33 days, including the 3-day screening and about 30-day follow-up.

7.1.5.7 Number of subjects required for clinical trial

A total of 366 eligible subjects are expected to be included in this clinical trial.

Among them, the first 60 subjects will enter the experimental group to use the experimental medical device for intervention; the case allocation will be based on the number of researchers/operators involved in the study, considering a maximum of 10 researchers/operators Involved in the study, the number of subjects assigned to each investigator/surgery was planned to be at least 6 cases.

The latter 306 patients were randomly enrolled and randomly assigned to the test group and the control group at a ratio of 2:1.

7.1.6 Effectiveness evaluation method

7.1.6.1 Description of Description of effectiveness indicators

(1) Primary effectiveness evaluation indicator: the time to hemostasis.

The time to hemostasis is defined as the time from the sheath removal to the time to achieving hemostasis for the subject. The “hemostasis” here refers to that, at the pucture site, there is no pulsating bleeding, nor expansionary/progressive hematoma.

(2) Secondary effectiveness evaluation indicators: Time to ambulation, procedure success rate, device success rate and length of stay (for patients receiving a diagnostic procedure).

- Time to ambulation: it is defined as the time from the sheath removal to the time that the patient can walk about at least 6 meters (or 20 steps).
- Procedure success rate: it is defined as successfully achieving hemostasis using the investigational medical device or control methods (including but are not limited to the assigned therapeutic method and other supplementary means) with absence of major complications;
- Device success rate: The device is successfully removed in accordance with the standard operating procedure (only the test group is evaluated);
- Length of stay: it is defined as the time from the sheath removal to the time the patient is discharged (for patients receiving a diagnostic procedure).

7.1.6.2 Selection of method and time to evaluate, record and analyze the effectiveness parameters

(1) Primary effectiveness indicator: the evaluation time point of the time to hemostasis is at Visit 2; interventional diagnosis and treatment and hemostasis (Day 1). The time from the sheath removal to the time of achieving hemostasis is recorded for each subject. The difference in time to hemostasis between the test group and control group is evaluated, so as to explore whether the time to hemostasis in the test group is superior to the control group.

(2) Secondary effectiveness evaluation indicators:

- Time to ambulation: the evaluation point is at Visit 3: Off-bed visit (Day 1-2); the time to ambulation is recorded for the subjects in each group. The difference in time to ambulation between the test group and control group is evaluated.
- Procedure success rate: the evaluation time point of procedure success is at Visit 2: interventional diagnosis and treatment and hemostasis (Day 1); the percentage of subjects with procedure success in each group is recorded. The difference in procedure success rate between the test group and control group was evaluated.
- Device success rate: the evaluation time point of device success is at Visit 2: interventional diagnosis and treatment and hemostasis (Day 1); the percentage of subjects with device success in each group is recorded.

- Length of stay: the evaluation time point of length of stay is at Visit 4: Discharge visit (on the same day of discharge). The length of stay of the subjects receive a diagnostic procedure (in test group and control group) is evaluated. The difference in length of stay between two groups is evaluated.

7.1.7 Safety evaluation method

7.1.7.1 Description of safety parameters

(1) Primary safety evaluation indicator: major complication rate.

Major complications are defined as:

1) Vascular injury or vascular repair required (through the surgical operation, angioplasty, ultrasound-guided hemostasis by compression or other means);
2) Permanent access site-related nerve injury;
3) Access site-related nerve injury requiring a surgery;
4) Access site-related bleeding requiring transfusion;
5) New ipsilateral lower extremity ischemia discovered by physical examination, Doppler ultrasonography or computer tomogrphy angiography, which requires invasive/non invasive intervention;
6) Local access site-related infection combined with fever, elevated white blood cell counts, pyemia, and evidence of local access site-related infection and discharge of pus, as well as positive blood culture, which requires (i) prolonged length of stay during the stay in hospital, or hospital readmission after discharge, and (ii) intravenous antibiotic therapy and/or surgical intervention (with the exception of incision and drainage under topical anesthesia);
7) Classic signs/ symptoms occurred in a short time after receiving the specified hemostasis procedures and generalized infection with positive blood culture, sepsis, which requires the intravenous antibiotic therapy;
8) Inflammatory reaction, including the local reaction and discharge of pus, which requires hospital readmission, and/or therapeutic or prophylactic intravenous antibiotic therapy, and/or surgical intervention (including the incision and drainage) to improve the conditions; without fever, elevated white blood cell counts, local negative blood culture (with the exception of normal microflora that is less correlated with the infection).

(2) Secondary safety evaluation indicators: minor complication rate, incidence of adverse events and severe adverse events.

- Minor **complications** are defined as:

1) Arteriovenous fistulae confirmed by the Ultrasonography or CT scan;
2) Pseudoaneurysm – Not requiring treatment;

3) Pseudoaneurysm - Treated with ultrasound-guided thrombin injection or Pseudoaneurysm - Treated with ultrasound-guided fibrin glue injection;
4) Hematoma at access site ≥6 cm;
5) Access site-related bleeding requiring >30 min to achieve hemostasis;
6) Late access site-related bleeding (post-discharge);
7) Ipsilateral lower extremity arterial emboli;
8) Transient loss of ipsilateral lower extremity pulse;
9) Ipsilateral deep vein thrombosis;
10) Transient access site-related nerve injury;
11) Access site-related vessel laceration;
12) Access site wound dehiscence;
13) Local access site-related infection combined with fever, elevated white blood cell counts, and evidence of local access site-related infection and discharge of pus, as well as positive blood culture, which requires the oral antibiotic therapy (or intravenous antibiotic therapy of less than 2 days) and/or incision and drainage under topical anesthesia;
14) Superficial inflammatory reaction, including the local symptom and discharge of pus, which requires the therapeutic or prophylactic oral antibiotic therapy; without fever, elevated white blood cell counts, local negative blood culture (with the exception of normal microflora that is less correlated with the infection).

- The definitions of adverse events and severe adverse events can be seen in the Section 13 “Rules of adverse event and device defect reporting”. All complications shall be recorded and reported as adverse events.

7.1.7.2 Selection of method and time to evaluate, record and analyze the safety parameters

(1) **Primary safety indicators:** the visit time point is set to the Visit 2: interventional diagnosis and treatment and hemostasis (Day 1), Visit 3: Off-bed visit (Day 1-2), Visit 4: Discharge visit (on the same day of discharge), Visit 5: Post-discharge follow-up (Day 30±7); the major complications are analyzed and recorded by the investigators, and the relevant corrective actions are taken. To evaluate whether the major complication rate in the test group is not inferior to that in the control group.

(2) **Secondary safety evaluation indicators:** the evaluation time point is at Visit 2: interventional diagnosis and treatment and hemostasis (Day 1), Visit 3: Off-bed visit (Day 1-2), Visit 4: Discharge visit (on the same day of discharge), Visit 5: Post-discharge follow-up (Day 30±7); the minor complications, adverse events and severe adverse events are analyzed and recorded by the investigators. The differences in minor complication rate and the rate of adverse

events and severe adverse events between the test group and control group are evaluated.

7.2 Study procedures

7.2.1 Study procedures

A total of 5 visits are included in this study, including the screening period (Day -7 - 0h), interventional diagnosis and treatment and hemostasis (Day 1), Off-bed visit (Day 1-2), Discharge visit (on the same day of discharge), Post-discharge follow-up (Day 30±7), etc. The study procedures are briefly described as follows:

7.2.1.1 Visit 1: Screening period (Day-7-0h)

This visit includes:

- Subjects voluntarily sign the informed consent form;
- Vital signs (pulse, blood pressure, respirations, temperature), physical examination;
- Record: medical history, treatment history (As for diseases and treatments other than femoral artery-related injuries, procedures, puncture, etc., the medical/ treatment history for at least one month prior to the procedure will be collected), allergy history, combined diseases and combined drug, demographic information, etc.;
- Confirm that patients will receive the cardiovascular interventional diagnosis and treatment. Record the reason/content (diagnostic/therapeutic) of interventional diagnosis and treatment;
- The preoperative examination includes:
  - Laboratory examination (within one week prior to interventional diagnosis and treatment): including the blood routine examination (PLT, WBC and HGB), blood biochemical examination (ALT, AST and ALB), coagulation function (fibrinogen, prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR) of prothrombin time); and the pregnancy testing for women with the fertility.
  - ECG examination (within 72 hours prior to interventional diagnosis and treatment).
- Review on the subject inclusion and exclusion criteria.

7.2.1.2 Visit 2; Interventional diagnosis and treatment and hemostasis (Day 1)

This visit includes:

- Record the vital signs: pulse, blood pressure, respirations, temperature;
- The patients receive the interventional diagnosis and treatment via common femoral artery. Record the model of the sheath that the patients used.

- Record the blood pressure after interventional diagnosis and treatment puncture;
- Confirm that the patients do not meet any of the intraoperative exclusion criteria, then randomize them into groups;
- Record the subjects' group and perform hemostasis using the investigational medical devices/control methods accordingly;
- Record the starting time of hemostasis;
- Record the completion time of hemostasis;
- Record all combined drugs, complications and adverse events during procedure and hemostasis;
- Record the device success rate;
- Record the procedure success rate.

7.2.1.3 Visit 3: Off-bed visit (Day 1-2)

This visit includes:

- Record the vital signs: pulse, blood pressure, respirations, temperature;
- Record the time to ambulation;
- Record all concomitant drugs, complications and adverse events.

7.2.1.4 Visit 4: Discharge visit (on the same day of discharge).

This visit includes:

- Record the vital signs: pulse, blood pressure, respirations, temperature;
- Record the subjects' length of stay;
- Record all concomitant drugs, complications and adverse events.

7.2.1.5 Visit 5: Post-discharge follow-up (Day 30±7)

This visit includes:

- Record the vital signs: pulse, blood pressure, respirations, temperature;
- Physical examination;
- Record all concomitant drugs, complications and adverse events in post-discharge periord.
- Laboratory examination: Blood routine (PLT, WBC, HGB), Biochemistry (ALT, AST, ALB)

7.2.2 Study flowchart

Study flowchart

Visit Items	Visit 1: Screening period (Day-7~0h)	Visit 2: Interventional diagnosis and treatment	Visit 3: Off-bed visit (d1~2)	Visit 4: Discharge visit (the same day of discharge)	Visit 5: Post-discharge follow-up (d30±7)

		and hemostasis (d1)			
Signing informed consent form	X				
Vital signs	X	X	X	X	X
Physical examination	X				X
Demographic data	X				
Inclusion/exclusion criteria	X	X			
Previous disease history, treatment history, and allergy history	X				
Co-administered Drug[a]	X	X	X	X	X
Electrocardiogram	X				
Laboratory examinations[b]	X				X
Reason/content of interventional diagnosis and treatment	X				
Grouping and device allocation		X			
Blood pressure after puncture		X			
Hemostatic operation		X			
Record the starting time of hemostasis		X			
Completion time of hemostasis		X			
Procedure success		X			
Device success[c]		X			
Time to ambulation			X		
Length of stay[d]				X	
Complications		X	X	X	X
Adverse event		X	X	X	X

a Concomitant drugs: collect the drugs administered to the subject after enrollment, with the exception of anesthetic and contrast medium required for interventional and diagnostic surgery.
b Specific tests are detailed in the test procedures at each visit; in order to avoid repeated tests, the lab tests 7 days before procedure can be accepted as screening lab tests.
c Only for subjects in the test group
d Only for subject receiving diagnostic procedure

7.2.3 Standard operating procedures of medical device

(1) Use of MynxGrip

Please read the IFU of the device carefully before using this device. The application of MynxGrip includes surgery preparation, device preparation, positioning balloon, deploying sealant and removing device. Do not use if the vascular closure device MynxGrip components or packaging appear to be damaged or defective or if any portion of the packaging has been previously opened. Do not reuse or resterilize. The vascular closure device MynxGrip is for single use only.

(2) Manual compression: Select a doctor who has experience in femoral artery compression to stop bleeding manually. Gradually apply pressure to the place with obvious femoral artery pulse above the puncture site, until it touches the artery pulse. Remove the sheath at the same time. Compress until there is no bleeding at the puncture site. Apply pressure with gauze and wrap up with elastic bandage. It is suitable to use the “8” figure-shaped bandaging method. Apply 1 kg of sandbag on it to compress the puncture site for 6 h. After surgery, the time to ambulation of lesioned limbs of the patient should be 12-24 h. [9]

7.3 Monitoring plan

Monitoring before the study mainly includes: delivery of the investigational medical device to the study sites, preparation of study documents, study personnel training; monitoring during the study mainly includes: subject screening, signing of ICF, laboratory inspection, regular visits, documents to be submitted to the institution and Ethics Committee during the study, adverse event monitoring; monitoring after end of (or before prematurely terminating) the study mainly includes: investigational medical device recycling and destruction, data query, validation of study documentation integrity, ethics committee notification, AE and SAE review, study site closure and clinical trial report.

The sponsor authorizes the Clinical Research Associate from Kuntuo Medical Research & Development (Beijing) Co., Ltd. to conduct the monitoring of this clinical trial.

The Clinical Research Associate shall have relevant professional background in fields of clinical medicine, pharmacy, biomedical engineering and statistics, etc., receive the

necessary training, be familiar with the Good Clinical Practice for Medical Devices and related regulations, know well about the non-clinical data of the investigational medical device and the clinical data of similar products, and the clinical trial protocol and its relevant documents.

The Clinical Research Associate shall comply with the GCP principles, supervise and urge the implementation of clinical trial, ensuring the clinical trial is strictly conducted as per the protocol, and the study data are true, complete and accurate. The specific responsibilities include:

(3) Verify that the study sites have qualifications, including the manning and training, well-equipped laboratory facilities in good working conditions, sufficient number of subjects, and investigators are familiar with the trial requirements;

(4) Monitor whether the study sites and investigators are in compliance with the study protocol, GCP and related regulations during the early, middle and later period of the trial;

(5) Confirm that all subjects have signed the informed consent form before participating into the trial. Familiar with enrollment rate of subjects and the progress of the trial. Be aware of any follow-ups, tests, examinations not yet done by investigators, and whether mistakes and unfinished events are corrected, and record these in details. In case of revision on the Informed Consent Form, make sure the subjects whose follow-up has not been finished to resign the ICF;

(6) Make sure that all CRFs have been filled out correctly and completely, and are consistent with the original data. All errors and unfinished events are corrected or noted, affixed with date and the signature of the investigators. Confirm and record the type of diseases, total number, gender, age of the subjects and therapeutic effect in each test.

(7) Verify that withdrawals from study or incompliance with requirements of ICF are recorded, and discuss these cases with the investigators;

(8) Verify that all adverse events and device defects are put on record; the severe adverse events and the device defects that may cause severe adverse events are reported within the specified time and be put on record;

(9) Be responsible for monitoring the supply, storage, use and maintenance of the investigational medical devices, as well as the handling process of these devices after trial;

(10) Ensure that maintenance and calibration of the relevant instruments for clinical trial are regularly conducted and those processes are recorded.

(11) Ensure that all clinical trial related documents the investigators received are the latest version;

(12) Results of each monitoring must be reported in written to the sponsor, including the date and time of monitoring, the name of CRA, name of study site, investigator's name, items inspected, progress of study, findings, facts, deviations identified during monitoring and which the conclusions, and the correction for errors and unfinished events.

8 Statistical considerations

8.1 Statistical design, method and analysis procedure

Unless otherwise stated, the continuous data is indicated in mean, standard deviation, quartile, minimum and maximum value; the categorical data is indicated in frequency and percentage.

The detailed statistical analysis method can be seen in Section 8.7. The statistical analysis method will be further explained in the statistical analysis plan.

All statistical analysis will use SAS 9.4 version and will be conducted when the database is locked according to the final statistical analysis plan.

8.2 Calculation of sample size

The total sample size is calculated based on the major complication rate. Assuming that the major complication rate in the test group is 2.1%, and the control group is 5%, with non-inferiority margin of 4%, one-tailed significance level of 0.025, power of test of 80%, and the randomization ratio between test group and control group is 2:1, then a total of 171 subjects are required for the test group and 86 for the control group. Considering a 15% of drop-out rate, then a total of 306 subjects will be included, with 204 in test group and 102 in control group; another consideration is to control the investigator's operational bias. Before the start of the randomized trial, 60 additional eligible subjects will be added, and the test group will be used directly to stop bleeding. The 60 subjects will complete follow-up according to the program requirements. The data will be analyzed separately for safety and will not be combined with data from formal trial subjects (306).
In summary, 366 eligible subjects are expected to be enrolled in the study.

8.2.1 Total Sample Size

8.2.2 Cases for each type of disease and reason for determination in clinical trial

The target population of this study is the subject who are going to receive interventional diagnostic or endovascular procedures via common femoral artery. There are different types of surgical procedures. Since hemostasis for the puncture site of the common femoral access does not tend to be greatly affected by different surgical procedures,

the number of subjects in different surgical procedures is not proportionally allocated, but there should be least 20% of the subject who are going to receiving interventional treatment.

8.2.3 Minimum and maximum number of subjects in each study site and reasons for determination

A total of 6 study sites participate in this study, with an average of 51 subjects each, which may range from a minimum of 26 to a maximum of 77.

8.3 Significance level and power of the clinical trial

(1) With regard to the superiority test for the primary effectiveness indicator — the time to hemostasis, as well as the non-inferiority test for the primary safety indicator — major complication rate, the one-tailed hypothesis test is conducted, the significance level of α=0.025, and the power of 1-β=0.8.

(2) For other hypothesis tests, the significance level is two-tailed α=0.05.

8.4 Expected drop-out rate

The expected drop-out ratio is not higher than 15%.

8.5 Acceptance/rejection criteria of study results

8.5.1 Effectiveness indicator

To evaluate whether the time to hemostasis for the puncture site of common femoral artery of the subjects in the MynxGrip group is superior to the control group, and compare whether there are statistical differences in the time to ambulation, procedure success rate and length of stay (for patients receiving a diagnostic procedure) between the two groups, and evaluate the device success rate of the test group.

8.5.2 Safety indicators

To evaluate whether the major complication rate of the subjects in MynxGrip group following hemostasis for the puncture site of common femoral artery is not inferior to the control group and compare whether there are statistical differences in minor complication rate, adverse events and severe adverse events between the two groups.

8.6 Criteria and reason for terminating the trial based on the statistical results

This trial does not include interim analysis and does not terminate the test according to statistical reasons.

8.7 Statistical method of all data, together with the handling method of missing, unused and error data (including termination and withdrawal halfway) and unreasonable data

8.7.1 Statistical analysis methods

8.7.1.1 Effectiveness indicator

- Primary effectiveness indicators

Time to hemostasis.

- Secondary effectiveness indicators

Time to ambulation, procedure success rate, device success rate, length of stay (for the patients received a diagnostic procedure).

8.7.1.2 Analysis method of effectiveness indicators

The statistical analysis for the effectiveness indicators is based on the full analysis set (FAS), and the sensitivity analysis is based on the per-protocol population set (PPS).

- Analysis method of primary effectiveness indicator

Conduct superiority test to evaluate the time to hemostasis. The null hypothesis and alternative hypothesis are as follows:

$$H_0: t_{test} - t_{control} \geq -5, \quad H_1: t_{test} - t_{control} < -5$$

Of which t_{test} is the average time to hemostasis of the subjects in the test group, $t_{control}$ is the average time to hemostasis of the subjects in the control group. To test for the superiority of the test group, the one-tailed 97.5% confidence interval of $t_{test} - t_{control}$ is constructed. If the upper confidence limit was less than -5min, we can reject the null hypothesis and accept the alternative hypothesis, considering that the test group is superior to the control group in time to hemostasis.

- Analysis method of secondary effectiveness indicators

For the procedure success rate, the Chi-squared Test or Fisher's Exact Test is used, according to the distribution characteristics.

For the time to ambulation, length of stay (for the patients received a diagnostic procedure), the t-test is used.

For the subjects in the test group, the device success rate and the percentage of subjects with procedure success are summarized.

8.7.1.3 Safety indicators

- Primary safety indicators

Major complication rate.

- Secondary safety indicators

Minor complication rate, adverse events and severe adverse events.

8.7.1.4 Analysis method of safety indicators

Statistical analysis of safety is based on the safety analysis set (SS).

- Analysis method of primary safety indicators

The non-inferiority test for the primary safety indicator of major complication rate is conducted. The null hypothesis and alternative hypothesis are as follows:

$$H_0: P_{test} - P_{control} \geq \Delta, \quad H_1: P_{test} - P_{control} < \Delta$$

Of which P_{test} is the major complication rate in the test group, and the $P_{control}$ is the major complication rate in the control group, $\Delta$is the non-inferiority margin of 4%. To test for non-inferiority of the test group, the one-tailed 97.5% confidence interval of $t_{test} - t_{control}$ is constructed. If the upper confidence limit is less than Δ, we can reject the null hypothesis and accept the alternative hypothesis, considering that the test group is not inferior to the control group in major complication rate.

- Analysis method of secondary safety indicators

For the secondary safety indicator of minor complication rate, the Chi-squared Test or Fisher's Exact Test is used, according to the distribution characteristics.

The secondary safety indicators of adverse events and severe adverse events are summarized and analyzed in the table. The degree of the adverse events occurred to cases in each group and its relationship to the device are described.

8.7.2 Handling of missing data

For effectiveness and safety indicators, missing data is not necessary to make up. The rules of making up the incomplete date will be further explained in the statistical analysis plan.

8.7.3 Handling of unreasonable or wrong data

The unreasonable or wrong data in the database will be identified and solved in the data management process.

8.8 Reporting procedure of deviation from original statistical plan

Before the database is locked, the changes to the statistical method in this protocol will be recorded in the statistical analysis plan. After the database is locked, the changes to the content in the final statistical analysis plan will be recorded in the statistical analysis report and clinical trial report.

8.9 Selection criteria and reason of subjects included in the analysis

(1) Full analysis set (FAS): in accordance with the Intention To Treat principle, it includes all subjects randomized into groups and then received treatment.

(2) Per-protocol population set (PPS): include all subjects in FAS that no major protocol deviation event affecting the effectiveness evaluation occurred.

(3) Safety set (SS): it includes all subjects randomized into groups, received treatment and having safety data after treatment.

8.10 Exclusion of special information when verifying the hypothesis and reason (if applicable)

None

9 Data management

9.1 Data collection

The electronic data capture (EDC) system will be used in this study. The study data will be entered into the eCRF by the investigators or authorized working personnel from the study site. Before inputting data by the study sites, proper training will be provided to the investigators or authorized working personnel from the study site, and information sacurity measures should be taken.

The investigators are responsible for maintaining all source documents, ensuring to receive the monitoring from the CRA at each visit. In addition, regardless of duration of the subjects' participation into the study, the investigators have to submit the complete eCRF for each subject participating into the study. Carefully check the study number and the subject number in all supporting documents (such as the laboratory records or study site records) that are submitted together with the eCRF. Remove all personal information (including the name of subject), or make it illegible, so as to protect the privacy of subjects.

9.2 Data entry and revision

All data will be input, corrected and modified by the investigators or their authorized personnel, which is not accessible to the CRA. The data in the eCRF is submitted to the data server. Any changes to the data will be recorded in the audit trace, so that the reason for the change, name of operator, modification time and date will be recorded. The role and privilege of the working personnel from the study site, who are responsible for data input, will be predetermined. If the data is questionable, the CRA or the data administrator will present the question in the EDC, and the working personnel from the

study site will be responsible for answering the question. EDC system will record the questionable audit trace, including the name of investigator, time and date.

9.3 Database locking

After the data is reviewed and the database established is confirmed correctly, the data is reviewed by the data manager, the main investigator, the statistical analyst, the sponsor and the supervisory manager, and the final definition and judgment of the analysis population is completed. After that, the data manager locks the database.

Databases or files that are locked may not be changed in general.

9.4 Data delivery

The database is locked, submitted to the statistical analyst, and then statistically analyzed according to the SAP. After the completion of statistical analysis, the statistical analyst will prepare the statistical analysis report and submit it to the principal investigator for writing the clinical trial report.

10 Feasibility analysis

10.1 Analysis of probability to success

This trial is conducted in accordance with the Declaration of Helsinki (18th General Assembly of World Medical Association, Helsinki, Finland, June 1964) and its latest revision (64th General Assembly of World Medical Association, Fortaleza, Brazil, October 2013), “Administrative Measures for Medical Device Registration” (2014), “Good Clinical Practice for Medical Devices (2016)”, etc. This protocol must be approved by the Ethics Committee before implementation. The subjects have to sign the Informed Consent Form (ICF) before participating into the trial, so that the subjects’ compliance will be guaranteed. Experiences from previous clinical trials of predicate products have shown that the drop-out rate can be well controlled.

The indications of the investigational medical device are clear. The composition and structure and the technical indicators meet the national industrial standards. This product has clear principles and definite in-vitro hemostasis effect. The product has passed the ex-factory inspection, and the registration test conducted by Jinan Quality Supervision and Inspection Center for Medical Devices, CFDA. It can be concluded that this product is a qualified for all its performance indicators have been certified.

At present, there are similar vascular closure device products available in the market and their effectiveness and safety had been demonstrated by some literature.

All study sits of this study are experienced in clinical trials with good quality control system. The investigators participating into the trial are experienced and skillful

clinicians Sufficient sources of subjects, strong research team structure, reasonable trial protocol, relatively short duration of study period, less risk of drop-out and loss of follow-up. unified personnel training, unified recording and evaluation criteria, normalized operation, precise recording and verification of observations and laboratory examination results during the clinical trial, all of these will ensure the authenticity and reliability of the study data and conclusions.

In conclusion, there is a strong possibility that this clinical trial will be successful.

10.2 Analysis of probability to failure

The trial is not implemented according to the trial protocol. The quantity of subjects is not sufficient. All operating procedures are not strictly performed. The record of all observations and laboratory examination results in the clinical trial is incomplete, lacking original supporting data.

The physicians experienced in interventional diagnostic or endovascular procedures and in use of vascular closure devices available in the market are selected as the investigators. Before this trial starts, the investigators should be trained on the product knowledge and operating procedures, ensuring skillful trial operating personnel. Through the participation into the clinical study, each patient will receive more extensive clinical follow-ups after undergoing the vascular closure. This extra supervision should be able to improve the probability of early detection of any possible adverse events. The overall monitoring for the medical records of each patient is conducted. The occurrence of complications is closely observed. The detailed handling pre-arranged planning is established.

For the device defects such as the damaged package and label falling off, etc. of the product for trial, the investigator should carefully inspect the product for trial before the trial. In case of any defects, the defective product should be suspended. If the device defect may affect the treatment of the subject or the outcome of disease, the investigator may suspend the trial and feed the identified problem back to the sponsor, until the sponsor can effectively solve this problem due to the device defect.

The investigator should record all adverse events occurred and device defects found during the clinical trial, work with the sponsor to analyze the causes of the events, form the written analysis report, make decision on whether to continue, suspend or terminate the trial, and report to the Ethics Committee through the Administrative Department for Clinical Trial of the study site for review.

In conclusion, there is a correlation between the failure of this clinical trial and the operation systemic risk, subjects' own factors, diseases and conditions.

11 Quality control of clinical trial

11.1 Quality control measures of the laboratory

The laboratories in the study should establish the standard operating procedure and quality control procedure of experimental observations.

11.2 Investigator training

Before the clinical trial starts, the responsible person of the study sites shall provide the training on trial protocol for the investigators.

11.3 Measures to improve the subjects' compliance

The investigator shall faithfully implement the informed consent, so that the subjects fully understand the trial requirements and work in conjunction with the trial.

11.4 Clinical trial audit

The Clinical Research Associate appointed by the sponsor shall regularly conduct monitoring on the study sites, making sure that all contents in the trial protocol are strictly followed. The raw materials are inspected to ensure consistent contents with the case report form (CRF).

11.5 Writing of case report form

All data input are in English. eCRF should be completed during or after the visits as soon as possible and kept up to date, making sure that it can reflect the up-to-date news of the subjects participating into the study. To avoid the difference in result evaluation between different evaluators, it should ensure that the baseline of the same subject and all subsequent effectiveness and safety evaluation are completed by the same person. The investigator shall review the data, so as to ensure the accuracy and correctness of all data entered into the eCRF. If some evaluations are not conducted in the study process, or some information is not available, applicable or unknown, the investigator shall record them in the eCRF. The investigator shall provide an electronic signature for the reviewed data. The original document refers to all records that are used by the investigator or study site, related to the subjects, and able to prove the existence of subjects, inclusion and exclusion criteria and its participation into this study, including the laboratory records, ECG results and subjects' folder, etc.

11.6 Storage of original data

The study site, investigator and sponsor shall establish a basic file archiving system. The basic documents of the clinical trial are divided into three parts according to the phases of clinical trials: document in trial preparation phase, documents in trial proceeding phase and documents upon termination or completion of trial phase. The

study site should properly keep the records and documents of clinical trial according to the agreement with the sponsor.

The original data of this trial include signed informed consent, test product release records, relevant laboratory inspection reports, case records and other related records. The study site shall keep the clinical trial data for up to 10 years after the completion of the clinical trial. The sponsor shall keep the clinical trial data until this medical device is no longer used. The Ethics Committee shall retain all related records for up to at least 10 years after the completion of the clinical trial.

For the selection method of the subjects, whether the information data regarding this trial which is provided to the subjects or their guardians is complete, whether the subjects can understand, whether the way to obtain the Informed Consent Form is proper; if necessary, the Ethics Committee shall organize the representatives from the subject group to test their level of understanding for the data, evaluate whether the informed consent is appropriate. The evaluation result should be recorded in written form and stored for up to 10 years after the completion of the clinical trial.

12 Clinical trial-involved ethical issues and informed consent

12.1 Ethical concerns

This clinical trial must be conducted in compliance with Declaration of Helsinki and relevant regulations of China's GCP. Before starting this clinical trial, the clinical trial protocol shall be approved by the Ethics Committee of the study sites where this clinical trial will be performed.

Before each patient is included into this study, the investigator is responsible for giving the patient or the patient-designated representative a complete introduction on the purpose, procedure and possible risks of this study in written form. Subjects should be informed that they have the right to withdraw from this study at any time. Prior to enrollment, a written Informed Consent Form must be provided for each subject. The investigators are responsible for obtaining the informed consent from each subject before he/she is enrolled into the study. The Informed Consent Form should be retained as the clinical trial document for future reference.

Before the clinical trial, the investigators need to submit the clinical trial protocol, informed consent form and other related documents to the Ethics Committee through Administrative Department for Clinical Trial of the study sites where the clinical trail is conducted. The clinical trials will begin only after the approval of the Ethics Committee. Any amendment to the protocol must be approved by the ethics committee before it

can be applied. Serious adverse events during the clinical trial should be submitted to the ethics committee in writing.

Before each study site starts the clinical trial, the Ethics Committee of the leading site shall be responsible for reviewing the ethical rationality and scientificity of the trial protocol. The Ethics Committee of other study site participating in the trial can employ the way of conference review or document review to review the feasibility of this trial in such study site on the prerequisite of accepting the review comment of the Ethics Committee of the leading site, including the qualification and experience of the investigators, equipment and conditions, etc. In general, it will make no suggestions for revision of the trial protocol design, but has the right not to approve the trial conducted in its study site.

The Ethics Committee shall supervise and keep track of the clinical trial of such study site. In case of any situations that the subjects' rights will not be protected perfectly, the Ethics Committee can request in writing to suspend or terminate this clinical trial at any time.

The suspended clinical trials shall not be resumed without the consent of the ethics committee.

The Ethics Committee shall retain all related records for up to at least 10 years after the completion of the clinical trial.

In case of any SAE, investigators should immediately take appropriate therapeutic measures for subjects, report the event in written to the Administrative Department for Clinical Trial of the study sites, and the study site then reports the event to the Sponsor. The Administrative Department for Clinical Trial should, within 24 hours, report the event to the Ethics Committee of the study site, as well as to the local food and drug administration and competent department of health and family planning of a province, autonomous region and municipality directly under the Central Government where the study site is located. For events regarding to deaths, study sites and investigators should provide all required data to corresponding Ethics Committees and Sponsor.

12.2 Approval of trial protocol

The approval of the clinical trial protocol is performed by the Ethics Committee, and clinical trials can be performed only after obtaining the final ethical approval.

12.3 Process of informed consent and text of informed consent form

Before the subjects participate into the clinical trial, the investigator shall fully inform the subjects or the guardian of the subjects without or with limited capacity for civil acts, of this clinical trial, including the known or foreseeable risk, possible adverse events, etc. Being fully aware of this clinical trial, the subjects or the guardian will sign and date

the Informed Consent Form. The investigator also needs to date and sign the Informed Consent Form.

The informed consent is jointly signed by the investigator and subject per se or his legal deputy in duplicate, each copy for each party.

In clinical trials, when investigators found adverse events other than those anticipated by medical devices, they should modify the relevant content of the informed consent agreement with the sponsors. After reporting to the ethics committee to review and consent in accordance with the relevant work procedures, the affected subjects or their guardian resign and confirm the informed consent amended;

13 Regulations of adverse event and device defect reporting

13.1 Adverse event

13.1.1 Definition of adverse event

An AE is defined as any untoward medical occurrence in the process of clinical trial, regardless of its relationship to the investigational medical device.
The adverse events occurred during the period from the time after completion of the diagnostic or interventional procedure to the time of the termination of the trial of the subjects participating in the trial should be reported (i.e. completion of 30-follow-up or withdraw the Informed Consent Form in the middle).

13.1.2 Determination of the severity of adverse event

The process, degree, handling and outcome of the adverse events should be observed in details, and be filled in the Adverse Events Report From. According to the following standards, the severity of adverse events can be classified into mild, moderate, and severe (Refer to the 2009 HHS/ NIH/ NCI Common Terminology Criteria for Adverse Events [CTCAE] version 4.0.3).
Mild: little or no treatment required, no impact on the subject's daily activities (instrumental activities of daily living, including cooking, buying clothes, using the telephone, financing, etc.; and personal daily activities of daily living, including bathing, dressing and undressing, eating, washing, taking medicine, etc., and ambulation).
Moderate: causing inconvenience of low level to the subject or subject’s concerns about treatment. Moderate events may have some impacts on physiological functions.
Severe: interrupting the subject's usual activities and requiring systemic medication or other treatment. Serious events are usually potentially life-threatening or disabling. Please note that term "severe" is not equivalent to "serious".

13.1.3 Determination on relationship between adverse events and instruments

The causality between the adverse event and the device shall be adjudicated according to the evaluation criteria used in NIH-FDA Clinical Trial Protocol Template-v1.0 7 Apr 2017, and be graded as follows:

- Definitely related: there is a clear evidence to suggest a causal relationship and alternative etiologies can be excluded. If a clinical event, including abnormal laboratory test results, which has a temporal relationship with conduct of the study intervention, cannot be explained by concurrent disease or other drugs or chemical agents, and is resolved or disappear after the study intervention is stopped (de-challenge), it is clearly a pharmacological or symptomatic event. If necessary, a reasonable re-challenge procedure shall be carried out (to observe whether the AE occurs again after the device is reused).
- Probably related: There is evidence to suggest the adverse event has a causal relationship with the study intervention and is not likely caused by alternative etiologies. If a clinical event, including abnormal laboratory test results, has a temporal relationship with conduct of the study intervention, may be explained by concurrent disease or other drugs or chemical agents, and is resolved or disappear after the study intervention is stopped, this adjudication can be made without re-challenge (to observe whether the AE occurs again after reusing the device).
- Possibly related: There is some evidence of a causal relationship (e.g., the event has a reasonable temporal relationship with the study medication). However, other factors may also contribute to the event (e.g., the subject's clinical condition, other concomitant events). Although the AE may be adjudicated to “have reasonable possibility to be related” soon after appearance, but it requires more information to make a judgment and, where appropriate, the event will be changed to "Probably related" or "definitely related".
- Unlikely related: a clinical event, including abnormal laboratory test results that may not be temporally related to the conduct of the study intervention (e.g., there is no reasonable temporal relationship between the occurrence of the event and the conduct of the study intervention), and can be reasonably explained by other drugs or chemical agents or related diseases (e.g., subject's clinical condition, other concomitant therapy).
- Unrelated: AE is completely independent from the study intervention, and/ or there is evidence that the event is definitely related to an alternative etiology. At this time, the clinician has to record an alternative etiology.

13.1.4 Records of adverse events

All adverse events during the study period must be recorded truthfully in the adverse event table. The investigator should conduct treatment and follow up specifically to the adverse events occurred until the symptoms disappear or are stable, work with the sponsor to analyze the causes of the events, form the written analysis report, make decision on whether to continue, suspend or terminate the trial, and report to the Ethics Committee through the Administrative Department for Clinical Trial of the study site for review The investigator shall preliminarily analyze the adverse events to determine whether they are the intraoperative adverse events, adverse events irrelevant to treatment or post-treatment adverse events.

13.1.5 Expected adverse events

In a study conducted overseas, a total 190 subjects were treated with Mynx Vascular Closure Device (the predecessor of the investigational medical device) for femoral artery puncture hemostasis, and the results showed following complications/adverse events: access site-related bleeding, with the occurrence rate of 0.5% (1/190); hematoma≥6 cm, with the occurrence rate of 3.2% (6/190); pseudoaneurysm – not requiring treatment, with the occurrence rate of 2.6% (5/190); pseudoaneurysm – treated with thrombin injection, with the occurrence rate of 0.5% (1/190); arteriovenous fistulae (n=2), ipsilateral deep vein thrombosis (n=1), and hematoma (n=1) which were concluded as irrelevant to the device. The clinical trial data of Mynx Vascular Closure Device can well predict the adverse events of the investigational medical device, MynxGrip.

In addition, other adverse events that may be involved in the femoral hemostasis treatment include: vascular injury, access site-related bleeding, access site-related nerve injury, ipsilateral lower extremity ischemia, access site-related infection and local access site inflammatory reaction, even generalized infection, ipsilateral lower extremity arterial embolism, transient loss of ipsilateral lower extremity pulse, ipsilateral deep vein thrombosis, etc. In addition, a long manual compression may lead to the body vagal reflex.

13.2 Device defect

The device defect is defined as unreasonable risk occurred under normal use of medical device during the clinical trial, which may do harm to the human health and life safety, such as label error, quality problem, fault, etc.

The investigator should record the device defects found in the process of clinical trial (All device deficiencies should be recorded in the eCRF), work with the sponsor to analyze the causes of the events, form the written analysis report, present the

comments on the continuation, discontinuation or termination of the trial. The report and comments will be reported, by the administrative department for clinical trial of medical device of study site, to the Ethics Committee for review.

The investigators and subjects can make complaints against the investigational product at any phase of this clinical study. The device defects that may cause severe adverse events need to be reported as required by the GCP.

13.3 Serious adverse events

13.3.1 Definition of serious adverse event

It refers to the event occurred in the course of clinical trials that lead to death or seriously deteriorated health, including:

- Fatal disease or injury;
- Permanent impairment of a body structure or a body function;
- Requiring in-patient hospitalization or prolongation of existing hospitalization;
- Requiring the medical or operative intervention so as to avoid the permanent defect in the physical structure or physical function;
- Leading to a fetal distress, fetal death or a congenital abnormality.
- Congenital defect, etc.

13.3.2 Reporting serious adverse event

In case of any SAE, regardless whether or not it is related to the investigational medical device, the investigators should immediately take appropriate therapeutic measures for subjects, report the event in written to the Administrative Department for Clinical Trial of the study sites, and the study site then reports the event to the Sponsor. The Administrative Department for Clinical Trial should, within 24 hours, report the event to the Ethics Committee of the study site, as well as to the local food and drug administration and competent department of health and family planning of a province, autonomous region and municipality directly under the Central Government where the study site is located. For events regarding to deaths, study sites and investigators should provide all required data to corresponding Ethics Committees and Sponsor.

The sponsor and the investigators shall investigate the SAE immediately and take necessary measures to protect the subjects' rights and interests, and report to the CFDA and the competent department of health and family planning at the same level where the device is registered within 5 workdays after being informed. The sponsor should also timely inform the other study sites and their investigators as well as the Ethics Committees of these study sites. For SAE concluded to be related to the

investigational medical device, the sponsor assumes the cost for the rescue of the subject, and the corresponding economic compensation.

In this study, the CRO, Kuntuo, will complete the report of the severe adverse events to the regulatory authorities on behalf of the sponsor, and inform the other study sites and investigators that participate into the trial.

13.4 Reporting procedure, contact information

In case of any serious adverse events and the device defects that may cause serious adverse events, investigators should immediately take appropriate therapeutic measures for subjects, report the event in written to the Administrative Department for Clinical Trial of the study sites, and the study site then reports the event to the Sponsor. In this study, the CRO, Kuntuo, will complete the report of the severe adverse events on behalf of the sponsor. Report contact: Kun Tuo Clinical Safety Management, E-mail: devicesafety@kuntuo.com, Tel.: 18601320939, Fax: 010-84492153.

14 Deviation from clinical trial protocol and procedures for revision of clinical trial protocol

14.1 Deviation from clinical trial protocol

The clinical trial must follow the GCP principles and comply with the trial protocol approved by the Ethics Committee; any intentional or unintentional acts that deviate from or violate the GCP principles or the trial protocol are called deviation from or violation against the protocol.

According to the responsibility body, it can be divided into: the deviation from the protocol due to the non-compliance of the investigators/research institutes, the subjects and the sponsor; according to the severity, it can be divided into: the slight and severe deviation from the protocol.

The slight deviation from the protocol is generally reported to the Ethics Committee at a regular basis. The cause, effect and handling measures of the event should be stated by the sponsor and/or investigator. When a severe deviation from the protocol occurs, it should be immediately reported.

There should be handling or improvement measures after each deviation from the protocol, so as to correct the error or avoid the recurrence of similar acts of deviation from the protocol.

14.2 Procedures for revision of clinical trial protocol

After this protocol is approved by the Ethics Committee, no revision can be made without prior consent of the Ethics Committee. If revision is necessary, a “Description on revision of protocol" signed by the principal investigator should be submitted to the Ethics Committee for approval;

The protocol after revision is acknowledged and signed by the sponsor.

15 Direct access to source data and document

The source data and source document in the Good Clinical Practice for Medical Devices (2016) are defined as follows:

The source data is defined as all information in the original record and its approved copy with regard to the clinical findings, observations and other activities in the clinical trial, which can be used for reproduction and evaluation of clinical trial.

The source documents are documents on which the source data is recorded, including printed, viewable or electronic documents.

In this clinical study, the principal investigator and its authorized investigator can access, generate and modify the out-patient medical records, subjects’ Informed Consent Form (ICF), eCRF, and original case records in the Hospital Information System (HIS). The laboratory inspection personnel and investigator can access and generate the inspection result report issued by them.

The data administrator can access and generate the data management data; the statistical analyst can access and generate the statistical analysis data.

The access and editor privileges of the rest of the data should be specified by the Standard Operating Procedure (SOP) of relevant department according to the requirements of relevant laws, regulations and technical specification in China.

16 Finances and insurance

The sponsor will sign up an agreement with the study sites for this study, in which financial matters and mode of payment are specified in details. See the agreement for details.

The sponsor will provide commercial insurance for the subjects included in the study. The sponsor will bear the treatment cost and relevant economic compensation for the clinical trial-related injury or death of subjects, with the exception of damages due to the fault of medical institution and medical staff in the diagnosis and treatment.

17 Contents that the clinical trial report should cover

According to the requirements in the Good Clinical Practice (GCP) for Medical Device (CFDA Order No. 25) jointly issued by the China Food and Drug Administration (CFDA) and National Health and Family Planning Commission of China (NHFPC), the contents to be covered in the clinical trial report include:

(I) General information;
(II) Summary;
(III) Synopsis;
(IV) Clinical trial objective;
(V) Clinical trial method;
(VI) Contents of clinical study;
(VII) General clinical information;
(VIII) Investigational medical device and control device or control diagnosis and treatment method;
(IX) Statistical analysis method and evaluation method used;
(X) Clinical evaluation criteria;
(XI) Organizational structure of clinical trial;
(XII) Ethical description;
(XIII) Clinical study results;
(XIV) Adverse events found in the clinical trial and their treatment;
(XV) Analysis and discussion of clinical trial results, especially the indications, scope of application, contraindications and precautions;
(XVI) Conclusion of clinical trial;
(XVII) Existing problems and improvement suggestion;
(XVIII) List of investigators;
(XIX) Other conditions that need to be described.

18 Confidentiality

The trial protocol is the confidential data. The trial protocol will be provided to the trial related working personnel of medical experts related to this trial, investigators participating in this trial, etc., and the related business entrusted institutions of the medical institution undertaking this trial, Ethics Committee and Contract Research Organization, etc. In addition to the explanation of the situation to the subjects, no contents of this trial should be uncovered or disclosed to a third party without the prior written consent of the sponsor. In addition, when part or all of the results of this clinical trial are published outside in the societies or journals, a written approval needs to be obtained from the sponsor.

This agreement and the contents of this clinical trial and all the attached information are confidential and belong exclusively to the sponsor, the investigator should be held responsible for confidentiality; including the patent application, the manufacturing process and unpublished data available to investigators provided by the sponsor, and so on, which should not be disclosed to any third party unless the consent of the sponsor is obtained and the obligation of confidentiality is valid after the termination or end of this test.

The investigator or his or her staff shall collect the personal data of the subjects and the data used for this study (“study data”), including the date of birth, gender, identity card, home address, pictures taken, and the personal data on your physical and mental health conditions, etc.

All medical records and study data that can be used to identify the subjects will be kept in secret within the scope of the law. However, the investigator, sponsor and its representative, Clinical Research Associate (a person who is responsible for examining how to carry out the study and ensure correct information collected), in certain circumstances, the administrative organization and Ethics Committee will examine and copy the confidential information that can be used to identify the subjects. All personal information in the study will be handled according to the national and local data protection act.

The subjects have the rights to ask the investigator and sponsor to protect their relevant information, and also have the rights to correct any inaccuracies in these data. If the subject withdraws his or her Informed Consent Form, the investigator will not use the data of the subject or disclose it to others, the sponsor may still use the study data obtained before the subject withdraws his or her Informed Consent Form.

The results of this study will probably be published in the medical journal and be introduced at the medical meetings. The subjects will not be identified in any of these publications.

19 Agreement on the publication of trial results

At the end of the trial, the leading site has the right to publish the final report as a research paper, the first author and corresponding author are the person affiliated to the leading site and the principal investigators of other study sites and the sponsor’s representative have the right of authorship.

20 Responsibilities undertaken by all parties

20.1 Responsibilities of the sponsor

(1) The sponsor is responsible for the initiation, application, organizing and monitoring of a clinical trial and is responsible for the truthfulness and reliability of the clinical trial. the sponsor is usually a medical device manufacturer. Foreign sponsor should authorize an organization in China as its agent according to the regulations.

(2) The sponsor is responsible for the organization to establish and modify the investigator's brochure, clinical trial protocol, informed consent form, Case Report Form, relevant standard operating procedure and other relevant documents, carry out the training required for the clinical trial.

(3) The sponsor shall, according to the characteristics of the investigational medical device, select the study sites and the investigators with qualifications. Before signing the clinical trial protocol with the study site, the sponsor shall provide the latest investigator's brochure and other relevant documents for the study site and investigators, for their decision whether they can undertake this clinical trial.

(4) The following main contents should be included in the investigator's brochure:

- Basic information of the sponsor and investigators;
- Brief introduction of the investigational medical device;
- Summary and conclusions that justify the intended use and the clinical trial design of the investigational medical device and
- Statement that the production of the investigational medical device is in compliance with requirements of Quality Management System for Medical Devices.

(5) The sponsor shall not exaggerate the function and effectiveness of the investigational medical device in the clinical trial protocol.

(6) During the clinical trial, in case of important information affecting the study process, the sponsor shall accordingly revise the investigator brochure and related documents in a timely manner, submit through the study site's administrative department of clinical trial of medical devices to the ethics committee for review and approval;

(7) The sponsor should sign up a written agreement with the study site and the investigator with regard to the clinical trial.

- The clinical trial should be implemented in accordance with the relevant laws and regulations, and will be monitored, audited and inspected;
- The data record and report procedure should be followed;
- The basic documents related to the trial should be kept for a period time of not less than the appointed time, until the sponsor informs the study site and investigators that this document is no longer needed;
- After the clinical trial is approved by the ethics committee, Sponsor shall provide the investigational medical devices for the study sites and investigators, and determine its transport conditions, storage conditions, storage time, shelf life and so on;
- The investigational medical device should be qualified, with a special label saying “for the trial” that is identifiable and encoded correctly. The investigational medical device should be properly packaged and stored according to the requirements of the clinical trial protocol;
- The sponsor shall establish the standard operating procedure related to the quality control of the clinical trial, such as the transport, receiving, storage, distribution, handling and recovery, etc. of the investigational medical device, for the study site and investigators to follow.

(8) The sponsor is responsible for the safety of investigational medical device in clinical trials. When the trial is found to affect the safety of the subjects or the trial implementation may change the approval of the ethics committee to continue the trial, the sponsor should immediately notify all study sites and investigators and deal with them accordingly.

(9) Where suspension or termination of the study is decided, the sponsor should notify all the administrative department for clinical trial of medical devices from all the study sites within 5 days, and give reasons in writing. The administrative department for clinical trial of medical devices from all the study sites should notify promptly corresponding investigators and ethical committees. The suspended clinical trials shall not be resumed without the consent of the ethics committee. Upon completion of study, the sponsor should report in writing form to the local food and drug administration at the provincial, autonomous regional and municipal level if necessary.

(10) Ensure that all investigators who implement clinical trials strictly follow the clinical trial protocol and correct any incompliance of the study sites and investigators with the relevant laws and regulations, the GCP of medical devices and the clinical trial protocols; in case of serious violation or absence of rectification,, the trial should be terminated and the report should be reported to the food and drug administrations of province, autonomous region and

municipalities directly under the Central Government where the study site is located and to the China Food and Drug Administration;

(11) The sponsor should bear the treatment cost and relevant economic compensation for the clinical trial-related injury or death of subjects, with the exception of damages due to the fault of medical institution and medical staff in the diagnosis and treatment.

(12) The sponsor bears the monitoring responsibility for the clinical trial and will select the qualified monitor to execute the monitoring responsibility. The number of the Clinical Research Associate and the times of monitoring depend on the complexity degree of clinical trial and the number of study sites participating into the trial.

(13) The Clinical Research Associate shall have relevant professional background in fields of clinical medicine, pharmacy, biomedical engineering and statistics, etc., receive the necessary training, be familiar with the Good Clinical Practice for Medical Devices and related regulations, know well about the non-clinical data of the investigational medical device and the clinical data of similar products, and the clinical trial protocol and its relevant documents.

(14) The Clinical Research Associate shall comply with the standard operating procedure of the monitoring of clinical trial of the investigational medical device, which is established by the sponsor, and supervise and urge the implementation of clinical trial in accordance with the protocol. The specific responsibilities include:

- Verify that the study sites have qualifications, including the manning and training, well-equipped laboratory facilities in good working conditions, sufficient number of subjects, and investigators are familiar with the trial requirements;
- Monitor whether the study sites and investigators are in compliance with the study protocol, GCP and related regulations during the early, middle and later period of the trial;
- Confirm that all subjects have signed the informed consent before participating into the trial. Get known about selection rate of subjects and the progress of the trial; Clearly and actually record the follow-ups failed to be completed by the investigators, trial not carried out, undone examinations, and whether to make corrections for the errors and omissions, etc.; For the revised Informed Consent Form, confirm that the affected subjects with unfinished clinical trial flow have resigned it;
- Confirm that all case report forms are completed correctly and in consistent with the original data; All errors and omissions are corrected or noted, which are also signed and dated by the investigators; The type of diseases, total number,

gender, age of the subjects, and therapeutic effect in each test. should be confirmed and recorded;

- Verify that withdrawals from study or incompliance with requirements of ICF are recorded, and discuss these cases with the investigators;
- Verify that all adverse events, complications and device defects are put on record; the severe adverse events and the device defects that may cause severe adverse events are reported within the specified time and be put on record;
- Be responsible for monitoring the supply, use, maintenance and transport, receiving, storage, distribution, handling and recovery of the samples of investigational medical device;
- Supervise the regular maintenance and calibration of related equipment used in the clinical trial process;
- Ensure that all the study documents provided to the investigators are the latest version;
- Results of each monitoring must be reported in written to the sponsor, including the date and time of monitoring, the name of CRA, name of study site, investigator's name, items inspected, progress of study, findings, facts, deviations identified during monitoring and which the conclusions, and the correction for errors and unfinished events.

(15) The sponsor, in order to ensure the quality of clinical trial, may authorize the trained skillful CRA who is independent of the clinical trials to validate compliance of the clinical trials to the GCP.

The validation can be regarded as the part of routine work of the sponsor's clinical trial quality control, and also can be used to evaluate the effectiveness of the monitoring activities, or carry out the inspection for the situations of severe or recurrent deviation from the clinical trial protocol, alleged counterfeiting, etc.

(16) The CRA shall develop the inspection plan and inspection procedures according to the importance of the clinical trial, quantity of subjects, type and complexity of clinical trial, risk level of subjects, etc.

(17) For the device defect that may cause serious adverse event, the sponsor should report to the CFDA and the competent department of health and family planning at the same level where the device is registered within 5 workdays after being informed. The sponsor should also inform other study sites and investigators that participate the trial, and timely inform the Ethics Committee of such study site through its administrative department for clinical trial of medical device.

(18) If the electronic clinical database or remote electronic clinical data system is used, the sponsor shall ensure the controlled and true clinical data, forming a complete verification file.

(19) For the multi-center clinical trial, the sponsor shall ensure that the protocol document has been established before the clinical trial, giving clear assignment of responsibility of the coordinating investigator and other investigators.

(20) For the multi-center clinical trial, the sponsor shall prepare the SOP according to the study protocol and organize the training on clinical trial protocol and the use and maintenance of investigational medical device for all investigators participating in the trial, so as to ensure the consistency in the implementation of clinical trial protocol, the use of investigational medical device.

(21) For the multi-center clinical trial, the sponsor shall ensure that the case report form is designed precisely and rationally, so that all the data from each study site are available to the coordinating investigator.

20.2 Responsibilities of the study sites

(1) The study site should evaluate the relevant resources according to the features of investigational medical device prior to the clinical trial, so as to decide whether to perform this clinical trial.

(2) The study site should properly keep the records and documents of clinical trial according to the agreement with the sponsor.

(3) The investigators in charge of clinical trials should meet the following requirements:

- With associate chief physician, associate professor, associate researcher or other senior professional titles and qualifications in the study site;
- Have the investigational product-related expertise and experience, and, where necessary, be well trained;
- Familiar with the requirements of, and the information and documents provided by, the sponsor; able to coordinate and administrate the personnel in the trial, familiar with the use of equipment, capable of dealing with adverse events and other events associated with the investigational medical device;
- Familiar with the relevant national laws and regulations and GCP of medical devices;

(4) The administrative department for clinical trial of medical device of study site should cooperate with the sponsor to apply to the Ethics Committee and submit the relevant documents prior to the clinical trial according to requirements.

(5) Investigators should ensure that the relevant staff involved in the trial are familiar with the principles, scope of application, product performance, method

of operation, installation requirements and technical specifications of the testing medical device, understand the nonclinical study data and safety data of the medical device used in the test, and grasp the possible risk prevention and emergency treatment methods of clinical trials;

(6) Investigators should ensure that all clinical trial participants are fully aware of the clinical trial protocol, the relevant regulations, the characteristics of the medical device used for testing, and the responsibilities associated with clinical trials, and ensure that a sufficient number of subjects who meet the criteria for inclusion in clinical trials are admitted to clinical trials, and ensure that there is sufficient time to implement and complete securely clinical trials in the agreed test period of the agreement according to the relevant provisions;

(7) The investigator should ensure to use the investigational medical device only for the subjects of this clinical trial, and may not charge any fee.

(8) Investigators should strictly follow the clinical trial protocol, without the consent of the sponsor and the ethics committee, or not in accordance with the provisions through the China Food and Drug Administration approval, shall not deviate from the protocol or substantial change protocol. Where there is presence of emergency in which the subject faces the direct safety risk and which needs to be immediately tackled, report can be submitted in writing afterwards.

(9) The investigator is responsible for recruiting the subjects, communicating with the subject or its legal representative. Investigators have a responsibility to explain to the subject the related details of the test medical device and the clinical trial, inform the subject of possible benefit and known, foreseeable risk, and obtain the signature and informed consent dated of the subject or his/her guardian;

(10) The investigator or other person involved in the trial shall not compel or induce the subject to participate in the trial in any other improper manner;

(11) In clinical trials, when investigators found adverse events other than those anticipated by medical devices, they should modify the relevant content of the informed consent agreement with the sponsors. After reporting to the ethics committee to review and consent in accordance with the relevant work procedures, the affected subjects or their guardian resign and confirm the informed consent amended;

(12) The investigators are responsible for making medical decisions related to clinical trials. In the event of adverse events associated with clinical trials, the study site and the investigator should ensure that the subject is provided with adequate and timely treatment and management. The investigator should

inform the subject in time when the subjects suffer from concurrent diseases requiring treatment and treatment.

(13) In case of any SAE, investigators should immediately take appropriate therapeutic measures for subjects, report the event in written to the Administrative Department for Clinical Trial of the study sites, and the study site then reports the event to the Sponsor. The Administrative Department for Clinical Trial should, within 24 hours, report the event to the Ethics Committee of the study site, as well as to the local food and drug administration and competent department of health and family planning of a province, autonomous region and municipality directly under the Central Government where the study site is located. For events regarding to deaths, study sites and investigators should provide all required data to corresponding Ethics Committees and Sponsor.

(14) The investigator should record all adverse events occurred and device defects found during the clinical trial, work with the sponsor to analyze the causes of the events, form the written analysis report, make decision on whether to continue, suspend or terminate the trial, and report to the Ethics Committee through the Administrative Department for Clinical Trial of the study site for review.

(15) The investigator should make sure that the clinical trial data is accurately, completely, clearly and timely recorded in the Case Report Form. Case report form is signed by the investigator, any data changes should be signed by the investigators and marked the date, at the same time the original record is retained and should be clearly identifiable;

(16) The study site and investigator should make sure that the data, documents and records generated in the clinical trial are true, accurate, clear and safe.

(17) The study site and investigator should accept and cooperate with the monitoring and audit of the sponsor, the supervision of the Ethics Committee, and provide all required records related to the trial When the food and drug regulatory authority and competent department of health and family planning send the inspection personnel to carry out the inspection, the study site and investigator should cooperate with the them;

(18) When the study site and investigators conclude that the risk outweighs the benefit or that the safety and effectiveness of the investigational medical device have been validated, and suspension or termination of the trial may be necessary, and it should be ensured that the subjects to receive the proper care and follow-up. The study site and investigator should also report in accordance with the regulations, provide the detailed written explanation. Relevant report

should be submitted to the local food and drug administration at the provincial, autonomous regional and municipal level if necessary.

When investigator is notified by the sponsor or the ethics committee to suspend of terminate the clinical trial, the subjects should be informed, and it should be ensured that the subjects to receive the proper care and follow-up.

(19) When study sites and investigators violate the relevant regulations or requirements of the sponsor and alter the experimental data and conclusions, they should be reported to the food and drug supervision and administration department of the province, autonomous region or municipality directly under the Central Government where the sponsor is and the State Food and Drug Administration;

(20) The investigator should ensure to complete all records and reports at the end of clinical trial. At the same time, the investigator should also ensure that the medical equipment received is consistent with the amount used, discarded or returned, ensuring that the remaining medical equipment is properly processed and documented;

(21) Investigators may, based on the need of clinical trial, authorize the relevant staff to undertake the subject recruitment, communication with subjects, , recording of clinical trial data, management of investigational medical device. The investigator shall provide training for the authorized persons and form the corresponding document.

Investigator's statement:

I agree that:

1. I will conduct this clinical trial in strict compliance with the Declaration of Helsinki, current laws and regulations of China, and the requirements of the protocol.
2. And record all required data accurately on the Case Report Form (CRF) and complete the final report of the clinical trial on time.
3. The investigational medical device will be used only for this clinical trial and the receipt and use of the investigational medical device will be recorded completely and accurately and the records will be retained throughout the clinical trial.
4. The monitor authorized or designated by the Sponsor and the regulatory authorities are allowed to conduct monitoring, verification and inspection for the clinical trial.
5. The clinical trial will be conducted in strict compliance with contract/articles of agreement signed by all parties.

I have already read the clinical study protocol, including the above statement and I fully agree all the above requirements.

Signature of investigator:

Date:

Comments of sponsor:
Signature (Stamp) Date: MM/DD/YYYY

Comments of investigator
Signature Date: MM/DD/YYYY

Comments of clinical trial institution of medical device
Signature (Stamp) Date: MM/DD/YYYY

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