A prospective multi-centre observational real-world Post-market European & Asian Registry with Low-profile Minos™ Abdominal Aortic Stent Graft (PEARL)

Name of device: Minos™ Abdominal Aortic Stent-Graft and Delivery System

Specification/Model: full specification

Version number and date: V1.0/2024-01-01

Manufacturer: Shanghai MicroPort Endovascular MedTech (Group) Co., Ltd.

Leading European unit: XXXX

Chief European investigator: XXXX

Sponsor: Shanghai MicroPort Endovascular MedTech (Group) Co., Ltd.

European sponsor: Lombard Medical Limited

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Protocol Summary

1、 Objective

To evaluate the clinical outcomes of the Minos™ Abdominal Aortic Stent-Graft and Delivery System in the treatment of Abdominal Aortic Aneurysm in a real-world patient population through a post-market observational registry.

2、 Design

The study is designed as a prospective, multi-centre, post-market, real-world observational registry study. Continuous enrollment is to be conducted for all subjects treated with Minos™ Abdominal Aortic Stent-Graft and Delivery System who meet the inclusion criteria and who voluntarily consent to participate in the study. An enrollment duration period of 24 months is expected for this project and initially, 200 subjects (170 in China and at least 30 in Europe) are to be enrolled. Patient follow up – including CT imaging - will be undertaken in accordance with the usual standard of care at participating sites, and is expected to occur at 30 days, 6 months, 12 months and 2-5 years post-procedure.

3、 Endpoints

1. Primary endpoint

- Technical success rate at 12 months

2. Secondary endpoints

- Incidence of major adverse events at 30 days
- Immediate technical success rate
- Incidence of successful aneurysm treatment at 2-5 years
- All-cause mortality up to 5 years post-procedure
- Aortic aneurysm related mortality up to 5 years post-procedure
- Secondary intervention rates up to 5 years post-procedure
- Aneurysm diameter and variation in aneurysm diameter from 30 days to 5 years post-procedure
- Incidence of type I, III endoleaks from 30 days to 5 years post-procedure
- The incidence rate of stent migration, fracture, stenosis, occlusion and distortion from 30 days to 5 years post-procedure

3. Other endpoints: technical success rate of Hercules balloon and incidence of balloon rupture, where applicable.

4、 Population

Eligible patients will be enrolled according to the inclusion criteria and the exclusion criteria from multiple study sites.

Inclusion criteria

To be enrolled, patients must meet all the following criteria:

- Diagnosis of infrarenal abdominal aortic aneurysm
- Plan to treat with Minos™ Abdominal Aortic Stent-Graft and Delivery System;
- Voluntary participation and completion of Informed Consent Form, with willingness to participate in follow-up to 5 years post-procedure.

Exclusion criteria

- Subjects in whom use of the Minos™ Abdominal Aortic Stent-Graft and Delivery System is contraindicated.

Indications:

- Abdominal Aortic Stent-Graft and Delivery System is indicated for the treatment of abdominal aortic aneurysms with a proximal neck length ≥15mm.

Contraindications:

- Severe stenosis or calcification near the aneurysm, leading to difficulty in achieving apposition of vessel wall and stent graft.
- Difficult access due to severe stenosis or tortuosity in the iliac artery or femoral artery
- Subjects with ruptured aneurysm or acute aneurysm
- Subjects with an infectious aneurysm.
- Those who are allergic to contrast agents or unable to tolerate contrast agents due to renal insufficiency.
- Patients with severe coagulation disorder and/or high risk of postoperative hemorrhage.
- Aneurysmal neck angulation greater than 60°
- Patients with blood supply to vital organs originating from the aneurysmal sac.
- Patients with other comorbidities and whose life expectancy does not exceed one year
- Subjects with connective tissue diseases, such as Marfan syndrome
- Minors and pregnant women
- Subjects who are allergic to nitinol
- Subjects who are considered not suitable for treatment with stent graft.

5、 Process

1. Case registration: The Internet registration system will be utilized to consecutively register all eligible patients who have been treated with Minos™ Abdominal Aortic Stent-Graft and Delivery System and voluntarily participated in the study.

2. Signing the Informed Consent Form

3. Case screening: Cases are selected according to inclusion and exclusion criteria

4. Case enrollment

5. Collecting the preoperative and intraoperative data

6. Postoperative follow-up: Imaging follow-up to be conducted in accordance with standard of care at participating sites, to include at 30 days, 6 months, 12 months and annually to 5 years after post-procedure. It is expected that all patients will complete this follow up schedule, but participants will not be excluded in the event that follow up is not completed.

7. Data analysis and summary: All relevant data will be collected and analysed from time to time as the study progress.

Flow chart of study:

Project	Visit1	Visit2	Visit3	Visit4	Visit5	Visit6	Visit（7-10）
Time points	**Preoperative**	**Intraoperative**	**Discharge**	**30 days after surgery**	**6 months after surgery**	**12 months after surgery**	**2/3/4/5 years after surgery**
Window period [3]				**±7d**	**±30d**	**±60d**	**±90d**
Informed consent [1]	**X**						
Demographics	**X**						
Inclusion criteria	**X**						
Baseline / Disease history	**X**						
Physical examination	**X**						
Blood test [2]	**X**		**X**				
CT	**X**			**X[4、5]**	**X[4]**	**X[4]**	**X[4]**
Record of operation process		**X**					
Evaluation of adverse event		**X**	**X**	**X**	**X**	**X**	**X**

Notes:

1. The subjects shall complete the signing of the Informed Consent Form before enrollment into the study. This will ideally be prior to the treatment procedure. The absence of laboratory test and imaging examination shall not be considered as a protocol deviation.
2. Blood examination includes standard of care tests in the study site, likely full blood count and standard liver and kidney function tests.
3. CT images collected outside of the follow-up window after surgery will not be considered as a protocol deviation.
4. CT imaging may not be undertaken at all follow up points if it is not the treating institution’s standard of care to do so. In such cases, alternative imaging can be recorded i.e. USS.
5. This study is an observational study. If the patient undergoes a postoperative CT review before discharge for clinical purposes or as part of the treating institution’s standard of care, this imaging examination will be accepted as the 30 days follow up CT, and a further CT scan at 30 days need not be undertaken.

Protocol text

1、 Sponsor information

Name of sponsor: Shanghai MicroPort Endovascular MedTech (Group) Co., Ltd.

Address: Building #1, 3399, Kangxin Road, 201318 Shanghai, People's Republic of China

Contact information: 021-38139300

Relevant qualification certificates:

Unified social credit code: 913101150512565326

2、 List of Study sites and Investigators

See Schedule 1 for details. If Schedule 1 is modified, then the version number of the protocol shall not be changed.

3、 Purpose and contents of study

3.1 Objectives

To evaluate the clinical outcomes of the Minos™ Abdominal Aortic Stent-Graft and Delivery System in the treatment of Abdominal Aortic Aneurysm in a real-world patient population through a post-market observational registry.

3.2 Project contents

The study is designed as a prospective, multi-centre, post-market, real-world observational registry study. Continuous enrollment is to be conducted for all subjects treated with Minos™ Abdominal Aortic Stent-Graft and Delivery System who meet the inclusion criteria and who voluntarily consent to participate in the study. An enrollment duration period of 24 months is expected for this project and initially, 200 subjects (170 in China and at least 30 in Europe) are to be enrolled. Patient follow up – including CT imaging - will be undertaken in accordance with the usual standard of care at participating sites, and is expected to occur at 30 days, 6 months, 12 months and 2-5 years post-procedure.

1. Primary endpoint

- Technical success rate at 12 months

2. Secondary endpoints

- Incidence of major adverse events at 30 days
- Immediate technical success rate
- Incidence of successful aneurysm treatment at 2-5 years
- All-cause mortality up to 5 years post-procedure
- Aortic aneurysm related mortality up to 5 years post-procedure
- Secondary intervention rates up to 5 years post-procedure
- Aneurysm diameter and variation in aneurysm diameter from 30 days to 5 years post-procedure
- Incidence of type I, III endoleaks from 30 days to 5 years post-procedure
- The incidence rate of stent migration, fracture, stenosis, occlusion and distortion from 30 days to 5 years post-procedure

3. Other endpoints: technical success rate of Hercules balloon and incidence of balloon rupture, where applicable.

In this study, immediate technical success rate, technical success rate at 12 months, secondary intervention rate, aneurysm diameter and variation in aneurysm diameter, and the incidence of type I and III endoleaks are used as efficacy indicators of the Minos™ Abdominal Aortic Stent-Graft and Delivery System. The incidence of 30-day major adverse events, all-cause mortality, aneurysm related mortality, stent migration, stent fracture, stenosis, occlusion and distortion are used as safety indicators of the Minos™ Abdominal Aortic Stent-Graft and Delivery System.

The presence of proximal endoleaks, and amount of vessel wall apposition will be assessed via immediate post-deployment angiography to determine whether balloon dilatation is indicated. The brand type of balloon will be voluntarily selected by investigators. If the Hercules balloon is used, data pertaining to the Hercules balloon shall be recorded. The success rate of Hercules balloon technique and the rate of balloon rupture are used as efficacy and safety indexes for Hercules balloon device. All relevant data will be collected and analysed from time to time as the study progress.

4、 Study background

Abdominal Aortic Aneurysm (AAA) refers to the localized expansion of abdominal aorta exceeding 50% of the diameter of normal abdominal aorta, of which the main complication is rupture and bleeding, and once ruptured, the mortality is about 90%[1]. The incidence rate of abdominal aortic aneurysm is growing year by year. Among the Asian population over 50 years old, the incidence rate of abdominal aortic aneurysm is 25.6%/100,000 in males and is 7.6%/100,000 in females; the incidence in men is about 3.5 times that of women[2]. There is no AAA-related epidemiological data in China, but the detection rate of abdominal aortic aneurysm in China is also increasing year by year with the aging of the population, the application of various imaging techniques and the improvement of clinical understanding.

Currently, clinical surgical treatments of subrenal AAAs mainly include traditional open surgery and endovascular abdominal aortic aneurysm repair (EVAR). Traditional open surgery has the disadvantages of massive trauma and many types of complications. It is usually not considered suitable for patients with heart, lung, kidney, brain and other organ lesions. In 1991, Parodi first reported the application of EVAR in the treatment of AAA. Compared with traditional surgery, it can minimize the degree of surgical invasiveness and reduce the surgical risk, so that the frail and ill patients with AAA can access their therapies and achieve better curative effect. It has become the preferred treatment for most patients [3-5].

EVAR has experienced significant and continuous technological changes and product updates within the last 30 years; however, it still presents several challenges, largely in the context of aneurysms with complex anatomy. For example, if the neck angulation is greater than 60 degrees or the landing zone is less than 15mm, the probability of endoleaks and chronic stent displacement is increased; There may also be an increased incidence of limb stent occlusion; vascular access site complications, arterial dissection, thrombosis or distal embolization as a result of iliofemoral tortuosity, stenosis, or aneurysm. Vascular access complications are directly related to the diameter of the graft delivery system. Studies have shown that a smaller diameter of the delivery system leads to a lower incidence of vascular access complications. Barbanti[6]*et al* conducted a comparative study on 14-18F and 19-26 F sheath devices in percutaneous arterial valve replacement procedures and found that the delivery sheath with lower profile is associated with lower vascular complications (1.0% vs 8.8%, $p< 0.001$), the incidence of life-threatening events and major bleeding events was 0.5% vs 5.4% ($p< 0.001$) and 2.5% vs 5.4% ($p = 0.046$), respectively.

Currently, there are only a few products available in the Chinese market, including Endurant, Excluder, and Zenith. The outer sheath of these device's delivery systems generally reaches 20F or 22F, and they are also expensive, which carries a heavy financial burden to patients. In order to benefit more patients in China and address the clinical challenges described above, Shanghai MicroPort Endovascular MedTech (Group) Co., Ltd. has developed the third-generation Minos Abdominal Aortic Stent-Graft and Delivery System based on the first-generation Aegis Bifurcated Abdominal Aortic Stent-Graft and Delivery System and the second-generation Hercules Bifurcated Abdominal Aortic Stent-Graft and Delivery System. The product adopts an ultra-fine delivery system, with an outer sheath diameter up to 14F. This system can help doctors locate the stent in the abdominal aortic aneurysm neck and iliac artery in a controlled, stable, and accurate way..

Pre-clinical testing was completed prior to CE marking and approval for use in the EU and a domestic pre-clinical investigation of the device in human patients was conducted following successful preclinical trials and testing. A total of 137 patients were enrolled, with an average age of 69.5 years. The 12-month clinical success rate was 89% (121 / 136), the rate of 30-day major adverse events was 1.5% (2/136), the 12-month all-cause

mortality was 7.4% (10 / 136), the aneurysm related mortality was 0.7% (1/136), and the safety and effectiveness have been verified. Therefore, the Minos™ Abdominal Aortic Stent-Graft and Delivery System has been authorized with the Registration Certificate for Medical Device of the People's Republic of China in March 2019, Certificate No.: GXZZ 20193130182.And was CE-Marked in September 2019, Certificate No.: M.2019.106.12584. On this basis, this post-market registry has been commenced to observe the medium and long-term clinical outcomes of Minos™ Abdominal Aortic Stent-Graft and Delivery System in the treatment of AAA in a real-world patient population.

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5、 Product features, structural composition, working principle, mechanism of action and scope of study

5.1 Product features

The abdominal aortic stent-graft and delivery system is used for the endovascular treatment of infrarenal abdominal aortic aneurysms. The product uses nitinol wires and polyester films as the basic implant materials and is composed of one body stent and two limb stents. The bare stent, barb, and neck at the proximal end of the body stent are designed to land in the aortic neck to reduce the risk of chronic displacement; The delivery system has an ultra-low profile; the diameter of the outer sheath of the body stent is 14F or 16F, and the diameter of the outer sheath of the limb stents is 12F. The surface has a hydrophilic coating. The stent graft can be introduced percutaneously through the sheath, which reduces the risk of trauma to the access blood vessel. The delivery system has a bare segment main body tip capture mechanism to allow accurate intraoperative positioning and safe and stable operability.

5.2 Structural composition

The abdominal aortic stent-graft and delivery system is composed of the stent-graft and a supporting delivery system. The stent-graft is composed of three modules: body stent-graft, CUFF stent-graft, and branch stent graft, the materials of which include the metal stents, graft, suture, release wire and the marker coil. The structure of the stent-graft is shown in Figure 1 and Figure 3.

The delivery system is used to facilitate the delivery, control and deployment of the stent-graft into the patient, and is mainly composed of the tapered tip, inner tube, multiple lumen tube, outer sheath, grip and other parts. The structure of the delivery system and the assembly position of the stent-graft in the delivery system are shown in Figure 2.

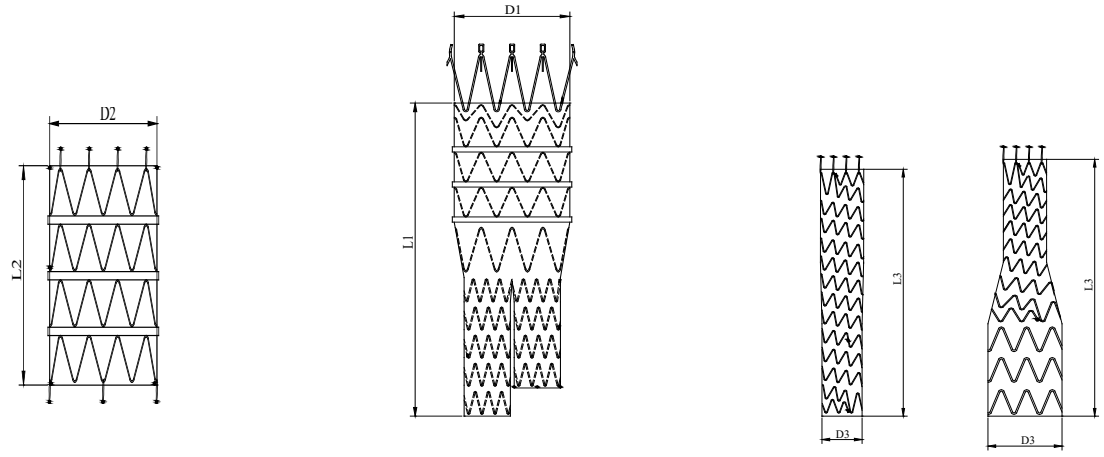
The body stent-graft has 12 marker coils, with 4 marker coils on the bare stent located at the proximal edge of the graft, 1 marker coil located at segment 3 and 5 of one ipsilateral limb respectively, 1 marker coil at segment 1 and 2 of the contralateral limb respectively, and 4 marker coils at the distal end of contralateral limb flush with the distal end of the graft.

The CUFF stent-graft has 6 marker coils, with 4 marker coils at the proximal end flush with the proximal end of the graft, and 2 marker coils at the distal end flush with the distal end of the graft.

The limb stent-graft has 2 marker coils, with 1 marker coil at the proximal end flush with the proximal end of the graft, and 1 marker coil at the distal end flush with the distal end of the graft.

At the proximal end of the outer sheath of the delivery system, there is a radiopaque ring made of platinum iridium alloy. The outer sheath of the delivery system is a non-hydratable catheter.

The specification and dimension of abdominal aortic stent-graft are represented by length L1, L2, L3 and diameter D1, D2 and D3, and its structure is shown in Figure 1. L1 represents the length of the ipsilateral graft of the body stent-graft; L2 represents the graft length of the CUFF stent-graft; L3 represents the graft length of the limb stent-graft; D1 represents the proximal diameter of the body stent-graft, D2 represents the diameter of the CUFF stent-graft, and D3 represents the distal diameter of the limb stent-graft.



a) CUFF stent-graft b) body stent-graft c) limb stent-graft

Figure 1 Structural diagram of the stent-graft

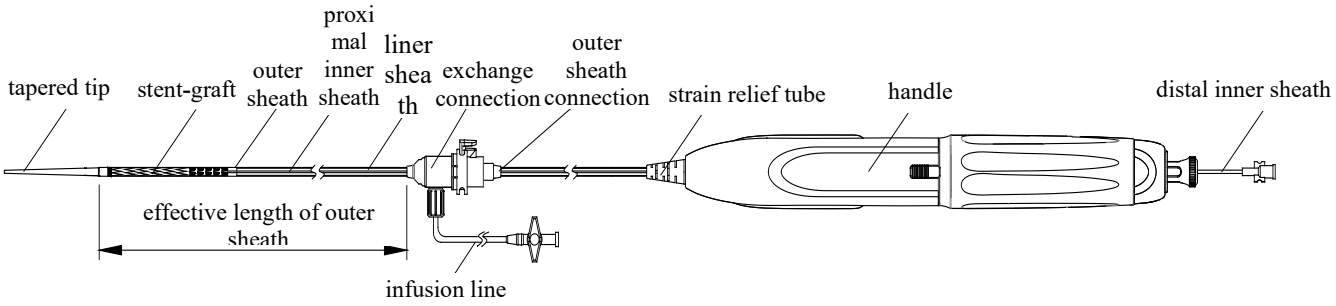


Figure 2 Structural diagram of the delivery system and the assembly position of the stent-graft

Refer to Figure 1 for the dimensions and specifications of stent-graft: L1, L2, L3, D1, D2 and D3 should be selected from the dimensions listed in Table 3.

Specification of stent-graft

Name	**Diameter (D) mm Tolerance±2**	**Length (L) mm Tolerance±5**
body stent-graft	22、24、26、28、30、32、34（D1）	90、100、110、120、130、140（L1）
Contralateral limb stent-graft	10、12、13、14、16、18、20、22、24（D3）	80、90、100、110、120、130、140（L3）
CUFF stent-graft	22、24、26、28、30、32、34、36（D2）	40 （L2）

Specifications of delivery system

Name	Optional size		Tolerance
Diameter of the outer sheath (French)	12F(4.0mm) 、14F(4.7mm)、16F(5.3mm)		±2F(0.66mm)
Effective length of outer sheath (mm)	14F、16F	550mm	±50mm
	12F	610mm	

5.3 Working principles and mechanism of action

Through the delivery system, the stent-grafts are deployed into the appropriate lesion site to isolate the aneurysm from the circulatory system and prevent aneurysm rupture. The aneurysmal vessel wall may shrink over time. Intimal cells permeate the pores in the graft material over time and eventually cover the stent-graft completely.

5.4 Scope of study

The study is being conducted in multiple centers in China, alongside a smaller number of centers in Europe, chiefly within vascular surgery departments and in those subjects with a definitive diagnosis of abdominal aortic aneurysm before surgery.

5.5 Risks

Please refer to the Design Failure Mode and Effects Analysis (DFMEA) Report (of Abdominal Aortic Stent-Graft and Delivery System) for details.

6、 Indications, contraindications, and precautions

6.1 Indications:

- Abdominal Aortic Stent-Graft and Delivery System is indicated for the treatment of abdominal aortic aneurysms with a proximal neck length ≥15mm.

6.2 Contraindications:

- Severe stenosis or calcification near the aneurysm, leading to difficulty in achieving apposition of vessel wall and stent graft.
- Difficult access due to severe stenosis or tortuosity in the iliac artery or femoral artery
- Subjects with ruptured aneurysm or acute aneurysm
- Subjects with an infectious aneurysm.
- Those who are allergic to contrast agents or unable to tolerate contrast agents due to renal insufficiency.
- Patients with severe coagulation disorder and/or high risk of postoperative hemorrhage.
- Aneurysmal neck angulation greater than 60°
- Patients with blood supply to vital organs originating from the aneurysmal sac.
- Patients with other comorbidities and whose life expectancy does not exceed one year
- Subjects with connective tissue diseases, such as Marfan syndrome
- Minors and pregnant women
- Subjects who are allergic to nitinol
- Subjects who are considered not suitable for treatment with stent graft.

6.3 Precautions

- Before using the product, physicians must be suitably trained in and have a clear understanding of the principle, clinical application, complications, adverse effects, and hazards of aortic stent graft surgery.
- This product comprises a main body stent-graft and delivery system, a contralateral limb stent-graft and delivery system, and a CUFF stent-graft and delivery system, all of which are packaged separately.

- The Abdominal Aortic Stent-Graft and Delivery System must have been disinfected and sterilized with ethylene oxide prior to release for clinical use.
- This product is for single use only. The company shall assume no liability or responsibility for any cross infection or other adverse consequences caused by reuse of the stent-graft, delivery system or any other component of the product.
- Do not use if the sealed package is found to be damaged.
- Please read the instructions carefully before use.

7、 Overall Design

7.1 Design

7.1.1 Study objectives

The purpose of this study is to observe the clinical outcomes of Minos™ Abdominal Aortic Stent-Graft and Delivery System in the treatment of abdominal aortic aneurysm in a real-world patient population, to assess its effectiveness and the acceptability of the risks inherent in its use, and to identify any new or emerging risks.

7.1.2 Method selection and its justification

Minos™ Abdominal Aortic Stent-Graft and Delivery System was granted a Registration Certificate for Medical Device in the People's Republic of China in March 2019, Registration No.: GXZZ 20193130182, and was CE-Marked in September 2019, Certificate No.: M.2019.106.12584. This post-marketing, real-world clinical trial will be conducted on this basis. The study is designed as a prospective, multi-centre, observational registry study. Following review and approval of the study protocol and patient informed consent form by the relevant local ethics committee, the Internet registration system will be used to register all patients treated with Minos™ Abdominal Aortic Stent-Graft and Delivery System who consent to participation in the registry. The investigators at participating study sites will determine the eligibility of patients for enrollment in the study according to the inclusion criteria. The participants and investigators will sign the Informed Consent Form as confirmation of the patient consenting to participation in the study. All participants will be followed up in accordance with the study protocol until 5 years after implantation.

7.1.3 Measures to avoid and reduce bias

This study will be conducted in multiple centers in and outside of China at the same time. The Internet registration system will be used to register all participants. Clinicians in each study site will select those patients that meet the inclusion criteria to minimize any selection bias created by selection of ineligible patients. Standard operating practices will be adopted to reduce performance bias. Objective index data will be collected as much as possible; design and quality control measures will be strictly investigated, sufficient contact with participants will be maintained as far as possible to maximize the follow-up data obtained and to minimize patients and data lost to follow up during the life of the study. The imaging data obtained from follow-up investigations will be evaluated by blind film reading method as part of the study's data analysis stage. The relevant indicators such as device related adverse events and serious adverse events will be determined by an independent Clinical Event Committee and independent data management and statistical analysis will be utilized to avoid evaluation bias.

7.1.4 Selection of subjects

Inclusion criteria

To be enrolled, patients must meet all the following criteria:

- Diagnosis of infrarenal abdominal aortic aneurysm
- Plan to treat with Minos™ Abdominal Aortic Stent-Graft and Delivery System
- Voluntary participation and completion of Informed Consent Form, with willingness to participate in follow-up to 5 years post-procedure.

Exclusion criteria

- Subjects in whom use of the Minos™ Abdominal Aortic Stent-Graft and Delivery System is contraindicated.

Indications:

- Abdominal Aortic Stent-Graft and Delivery System is indicated for the treatment of abdominal aortic aneurysms with a proximal neck length ⩾15mm.

- Contraindications:
  - Severe stenosis or calcification near the aneurysm, leading to difficulty in achieving apposition of vessel wall and stent graft.
  - Difficult access due to severe stenosis or tortuosity in the iliac artery or femoral artery
  - Subjects with ruptured aneurysm or acute aneurysm
  - Subjects with an infectious aneurysm.
  - Those who are allergic to contrast agents or unable to tolerate contrast agents due to renal insufficiency.
  - Patients with severe coagulation disorder and/or high risk of postoperative hemorrhage.
  - Aneurysmal neck angulation greater than 60°
  - Patients with blood supply to vital organs originating from the aneurysmal sac.
  - Patients with other comorbidities and whose life expectancy does not exceed one year
  - Subjects with connective tissue diseases, such as Marfan syndrome
  - Minors and pregnant women
  - Subjects who are allergic to nitinol
  - Subjects who are considered not suitable for treatment with stent graft.

Criteria and procedures for termination of the study/treatment

- Should severe safety concerns arise, the study shall be suspended in time.
- If the therapeutic efficacy of the investigational device is found to be poor or ineffective such that it is of no clinical value, the study shall be suspended.
- The discovery of major errors in the clinical trial protocol or significant deviation from it, making it difficult to evaluate the safety and efficacy of the investigational product.
- The sponsor requests suspension (for the reason of funds, management, etc.)
- Revocation is issued by the approving authorities.

Should the above-mentioned situations arise, the sponsor shall promptly inform the investigators, institutions and Ethics Committee of each study center. For subjects who have been treated with the study product, the sponsor shall fulfill the responsibility for the subjects during the study in accordance with the signed Informed Consent Form.

Planned enrollment date

This study is expected to start screening in October 2021, with patients in Europe recruited from early 2024, subject to local ethical committee approval.

Duration of the clinical trial and rationale

After the clinical trial is approved or filed by the Ethics Committee of the participating hospital, it will be registered on “clinicalstudy.gov” or Chinese Clinical trial Registry equivalent. It is expected to take 6 months for the registration, and then the subjects will be screened and enrolled. The expected enrollment period is 24 months, and the follow-up of 30 days, 6 months, 12 months, and 2-5 years will be completed as required. It is expected to take 6 months to summarize and analyze the data and form the statistical report and clinical summary report. Therefore, the overall duration of the clinical trial is anticipated to be approximately 8 years.

Expected duration of each subject's participation

After signing the Informed Consent Form, the subjects will undergo examination as required and imaging follow-up at 30 days, 6 months, 12 months and 2-5 years after surgery in accordance with this protocol. The expected participation time of each subject is 5 years.

Number of subjects required for the clinical trial

It is expected that 200 subjects will participate in this clinical trial.

7.1.5 Primary endpoint

Successful aneurysm treatment: on the basis of technical success and during the follow-up period, the absence of aneurysm rupture, continuous type I and III endoleaks after operation, aneurysm enlargement (aneurysm diameter increased by more than 5mm), secondary intervention due to endoleak, stent occlusion or migration, including open surgery and endovascular surgery. Expected secondary interventions will not be included in the analysis.

7.1.6 Secondary endpoints

30-day major adverse events: events that meet one of the following criteria during the study:

- All-cause mortality: death of any cause occurring within 30 days of procedure.
- Intestinal ischemia: lack of sufficient blood flow in the intestine, requiring intensive drug treatment or surgical/intravascular intervention treatment.
- Myocardial infarction: the increase of one or more cardiac biomarkers (especially troponin) with evidence of myocardial ischemia: ECG changes suggesting new ischemia, or imaging evidence.
- Paraplegia: severe paralysis of lower limbs.
- Kidney failure: GFR < 15ml/min, requiring permanent dialysis, renal transplantation, or death due to renal insufficiency.
- Respiratory failure: pneumonia or respiratory failure requiring ventilator support for more than 24 hours after surgery.
- Stroke: symptoms lasting 24 hours due to cerebrovascular diseases such as hemorrhage, embolism or thrombosis.
- Blood loss > 1000 ml: estimated intra-procedural blood loss > 1000 ml.

Immediate technical success: successful introduction and withdrawal of stent graft and delivery system, with accurate positioning of stent graft, normal stent shape, no distortion, bending, stenosis and occlusion, and no accidental coverage of internal iliac artery or visceral artery.

All-cause mortality: death from any cause.

Aneurysm related death: death caused by rupture of abdominal aortic aneurysm or any operation to treat abdominal aortic aneurysm. All deaths shall be judged by the Clinical Events Committee (CEC) to determine the relevance of aneurysm, instruments or surgery.

Secondary intervention: including open and intracavitary intervention. Open surgery: Open surgery performed at any time to address a failure of endovascular treatment due to failure of stent implantation or placement, complications or other clinical conditions, or after the initial success of endovascular treatment. Secondary endovascular intervention: any intravascular surgical intervention performed to resolve complications such as endoleak, aneurysm expansion, stent occlusion, stent migration and stent defect after the implantation of Minos™ system.

Change in aneurysm diameter: including “enlargement”, which refers to an increase of aneurysm diameter greater than 5mm; “reduction”, which refers to a reduction of aneurysm diameter greater than 5mm; and “stable”, which refers to a change in aneurysm diameter less than or equal to 5mm.

Endoleak: recorded after surgery according to imaging appearances. Adjuvant therapy such as balloon dilatation due to intraoperative endoleak shall not be included in the analysis. Type I endoleaks are leaks at the proximal or distal attachment sites. Type II endoleaks are caused by retrograde flow through collateral vessels into the aneurysm sac. Type III endoleaks are holes, defects, or separations in the stent-graft material. Type IV endoleaks represent porous graft walls. Endoleaks observed in the same subject at different follow-up timepoints without and which have not been treated shall be calculated once.

Stent migration: movement of stent greater than 10 mm.

Stent fracture: fracture of the metal wire of the stent framework.

Stent stenosis and occlusion: stenosis of the internal diameter of the covered section of the stent is a narrowing of ≥ 50% as seen on imaging; stent occlusion refers to 100% stenosis of stent detected on imaging.

7.1.7 Other endpoints

Technical success - Hercules balloon: successful introduction and withdrawal of balloon dilation catheter, with accurate balloon positioning, expected expansion diameter reached, no balloon rupture or leakage during operation, and no balloon-related vascular injury.

Balloon rupture: refers to the rupture of balloon dilatation catheter during dilation.

7.2 Study Process

1. Case registration: The Internet registration system will be utilized to register all eligible patients who are been treated with Minos Abdominal Aortic Stent-Graft and Delivery System and who have voluntarily consent to participate in the study.

2. Signing the Informed Consent Form

3. Case screening: Cases are selected according to inclusion and exclusion criteria;

4. Case enrollment

5. Collecting the preoperative and intraoperative data

6. Postoperative follow-up: Imaging follow-up to be conducted in accordance with standard of care at participating sites, to include at 30 days, 6 months, 12 months and annually to 5 years after post-procedure. It is expected that all patients will complete this follow up schedule, but participants will not be excluded in the event that follow up is not completed.

7. Data analysis and summary: All relevant data will be collected and analysed from time to time as the study progress.

Flow chart of study:

Project	Visit1	Visit2	Visit3	Visit4	Visit5	Visit6	Visit（7-10）
Time points	**Preoperative**	**Intraoperative**	**Discharge**	**30 days after surgery**	**6 months after surgery**	**12 months after surgery**	**2/3/4/5 years after surgery**
Window period [3]				**±7d**	**±30d**	**±60d**	**±90d**
Informed consent [1]	**X**						
Demographics	**X**						
Inclusion criteria	**X**						
Baseline / Disease history	**X**						
Physical examination	**X**						
Blood test [2]	**X**		**X**				
CT	**X**			**X[4、5]**	**X[4]**	**X[4]**	**X[4]**
Record of operation process		**X**					
Evaluation of adverse event		**X**	**X**	**X**	**X**	**X**	**X**

Note:

1. The subjects shall complete the signing of the Informed Consent Form before enrollment into the study. This will ideally be prior to the treatment procedure. The absence of laboratory test and imaging examination shall not be considered as a protocol deviation.
2. Blood examination includes standard of care tests in the study site, likely full blood count and standard liver and kidney function tests.
3. CT images collected outside of the follow-up window after surgery will not be considered as a protocol deviation.
4. CT imaging may not be undertaken at all follow up points if it is not the treating institution’s standard of care to do so. In such cases, alternative imaging can be recorded i.e. USS.
5. This study is an observational study. If the patient undergoes a postoperative CT review before discharge for clinical purposes or as part of the treating institution’s standard of care, this imaging examination will be accepted as the 30 days follow up CT, and a further CT scan at 30 days need not be undertaken.

7.3 Specifications for using the device

Refer to the Product Instruction Manual.

7.4 Monitoring plan

The following activities should take place:

- The CRF shall be checked based on the subject's original medical history and original records to ensure that the records are accurate, timely recorded and complete.
- Ensure that the study operation meets the requirements of the protocol and medical device regulations.
- Ensure that the study is conducted in accordance with the requirements of the Ethics Committee
- Ensure that the procedures for acquisition of Informed Consent Form meet the specifications.

- Conduct data monitoring for the selected subjects in each centre to ensure the authenticity and accuracy of the data.
- Complete the visit records of the centre and reasonably schedule the next visit, where necessary.

8、 Statistical Considerations

8.1 Population

Full Analysis Set (FAS): set of subjects that are determined according to the "Intention To Treat" principle. Refers to all subjects who signed the Informed Consent Form, met all inclusion and exclusion criteria and were treated with Minos™ system.

Per protocol set (PPS): subset of the full analysis set. Refers to all subjects in whom Minos™ system has been successfully implanted, in whom the main evaluation indicators can be observed, and in whom no significant deviations from the study protocol have been observed.

Safety set (SS): refers to all subjects who have been enrolled and evaluated for safety.

8.2 Method of statistical analysis

The SAS9.13 statistical software will be used for statistical analysis. The effectiveness analysis will be performed in Full Analysis Set and Per-Protocol Set; the demographic analysis at baseline will be performed based on the Full Analysis Set; the safety evaluation will be performed in Safety Set. Descriptive summary statistics will be provided for all data. For classified variables, the frequency, percentage and 95% accurate binomial confidence interval of for point estimation shall be calculated; for continuous variables, the mean, median, interquartile range and 95% confidence interval for point estimation will be calculated. All statistical analyses are performed at the bilateral 0.05 significance level.

Kaplan Meier survival analysis shall be performed for all-cause mortality, aneurysm-related mortality, incidence of secondary intervention and other safety indicators during follow-up period.

A complete analysis of all safety evaluations will be provided, including the following analysis:

- Total number of serious adverse events (SAE)
- Total number of device-related adverse events
- Total number of device-related serious adverse events
- Total number of adverse events (AE)
- Number and percentage of subjects with serious adverse events
- Number and percentage of subjects with device related adverse events
- Number and percentage of subjects with device related serious adverse events
- Number and percentage of subjects with adverse events

8.3 Sample size calculation

This study is an observational registration study - a descriptive study without comparison and formal hypothesis test, and the determination of sample size is not based on statistical considerations. The follow-up time and sample size are consistent with the overall objectives of the study. Considering the Guidelines for Clinical Trials of Aortic Stent-Graft System, the sample size is calculated to be 200 cases.

8.4 Criteria for termination of the study based on statistics

This study does not pre-establish interim analysis and the corresponding premature termination criteria, so this section is not applicable.

As a real-world study, the subjects will be followed up for 5 years. Periodic data statistical analysis is planned for 30 days, 6 months, 12 months, and 2-5 years post-procedure surgery. All statistical analyses shall be performed after the data have been collected, cleaned, and finally locked.

8.5 Procedures for processing missing, unused, incorrect or unreasonable data

Statistical analysis will be undertaken in accordance with the corresponding standard operating procedure (SOP). Refer to the relevant documentation for details. Incorrect data will be identified and rectified during the data cleaning process prior to statistical analysis. Data relating to patients who have withdrawn from the study will be included in the final statistical analysis. Specific reasons for all patients who have withdrawn from the study will be described in the statistical report. Missing data relating to the study's primary endpoint caused by premature withdrawal will be imputed in accordance with the above-mentioned strategy for missing values. This imputation process will not be performed for missing data relating to any other endpoints.

8.6 Subgroup analysis

In addition to analysis of the data recorded in the full analysis and protocol sets, several subtypes were predesignated, including but not limited to subset with neck length < 15mm and neck angle greater than 60°, for example.

9、 Data Management

9.1 Completion and transfer of Case Report Forms (CRF)

Electronic Case Report Forms (CRFs) will be used in this study, which will be filled in by the investigator or designated participating staff members at the study sites. A separate case report form must be completed for each participant at each time point described in this protocol. Following review of the completed CRFs by the monitor, the first copy shall be transferred to the data administrator for data entry and management.

9.2 Data entry and modification

Questions regarding data submitted on the eCRFs will be sent to the investigators via a query form (QF); the data administrator shall modify, confirm, and enter the data according to the answers of the investigators, and issue a further QF if necessary.

9.3 Database locking

After completing the data review and confirming the correctness of the established database, the data administrators, principal investigators, sponsor, and monitors shall jointly review the data and complete the final definition and determination of the analysis population. The database will then be locked by the data administrator. The locked database or file may not be modified thereafter.

9.4 Data processing

The locked database shall be provided to the statistical analysis personnel for statistical analysis.

10、Feasibility Analysis

The Minos^{TM} abdominal aorta stent graft and delivery system have undergone preclinical trial and testing and obtained medical device registration certificate in People's Republic of China, and CE certification in March 2019, September 2019, and 2017 respectively. It is therefore deemed to have met the relevant safety standards required by these certification methods.

The study sites participating in this study possess the necessary equipment and technical resources and have the required surgical experience in endovascular interventional therapy of aortic diseases to do so. The Principal Investigator at each site has sufficient clinical experience and academic status to undertake this role. Therefore, the study is expected to successfully achieve the objectives intended by the Sponsor.

11、Quality Control

11.1 Subject enrollment

All subjects enrolled in the study will be registered in the online registration system.

11.2 Training

Before the initiation of the clinical trial, relevant personnel should be trained, and investigators of each centre will conduct a kick-off meeting to carry out training on the clinical protocol, the informed consent process, the use of devices, the completion of documents and other aspects of the study. During the study, the investigators and relevant personnel should be trained specifically in local standard of care practices.

11.3 Monitoring

During the clinical trial, the clinical research associate or other individual nominated by the sponsor will visit each study center in person or remotely according to the clinical monitoring plan, if one is to be used. The purpose of such visits will in part be to ensure that all the contents of the protocol are strictly adhered to.

11.4 Audit

During the study, including during patient enrollment and follow-up, professional auditors may be appointed to review the progress of the study, to ensure the accuracy, completeness, and timeliness of the data, as well as the compliance of the clinical process with relevant regulations.

11.5 Storage of original data

Original data, including the signed patient informed consent forms, relevant laboratory test reports, case records and other relevant patient-related records shall be stored at each study site, in accordance with local and national policies. Data pertaining to the study shall be stored for not less than 10 years after the termination of study.

12、 Ethical protection and informed consent

12.1 Ethical considerations

This study will follow the ethical guidelines set out in the Helsinki Declaration of the world medical assembly.

All parties involved in the study shall bear corresponding ethical responsibilities according to their respective responsibilities in the study. In case of any of the following circumstances, the investigator shall promptly report to the relevant department of the study site, and promptly notify the lead study unit and the reporting Ethics Committee:

1. Serious adverse events

2. Any revision of the documents approved by the ethics committee does not affect the rights, interests, safety and health of the subjects, and non-substantive changes not related to the purpose or end point of the clinical trial do not need to be reported in advance, but shall be notified in writing afterwards

3. Suspension, termination, or request for resumption of study after suspension

4. Circumstances affecting the rights and interests, safety, and health of subjects or the scientific basis of the study.

To protect the rights, interests, safety, and health of participants, should a deviation from the protocol take place in an emergency setting that cannot be reported at the time of occurrence, it shall be reported in writing as soon as possible in accordance with relevant regulations.

Pregnant women, the elderly, people with intellectual disabilities and patients in life-threatening situations should be avoided as subjects as far as possible; when it is necessary to select such participants, this should be done in accordance with the study's eligibility criteria and must comply with the relevant additional requirements put forward by the ethics committee.

Before subjects consent to participate in study, investigators shall fully explain the details of it to the patient, or his/her family, guardian, or legal representative. These details must include known, foreseeable risks and any potential adverse events. Following this, the subject or his/her legal representative should sign their name and date on the informed consent form, and the investigator who obtains the informed consent is also required to sign their name and date on the informed consent form.

The informed consent form shall indicate the date of issue and the date of any subsequent revised version. If the informed consent form is revised during the study, the revised informed consent form should be reviewed and

approved again by the Ethics Committee before it is executed, where necessary. After a revised informed consent form has been approved and sent to the study sites, all subjects who have not completed the study must sign a copy of the new version of the informed consent form.

All subjects have the right to withdraw from the study at any stage without any financial responsibility and without providing a reason for this decision.

12.2 Review and approval of the protocol

This multicenter study will be conducted by multiple investigators in different clinical institutions at the same time and according to this same study protocol, following approval by the relevant local ethics committee. During the course of the study, should the study protocol, informed consent form, or other documents be revised, a deviation is requested, or the study is to be resumed following suspension, the implementation can be continued only after the written approval of the relevant the ethics committee is obtained.

12.3 Informed consent process and informed consent form

For incapacitated subjects, if the ethics committee agrees in principle, and the investigator believes that the subjects' participation in the study is in their interest, such patients may also be included in the study, but related documents shall be signed and dated by their legal guardian or legally acceptable representative before their participation in the study; Should none of the subject or his or her family, guardian, or legally acceptable representative have reading capability, a witness shall be present throughout the informed consent process. After the informed consent form has been explained in detail, the witness shall read the informed consent form to check for consistency with the orally informed contents, and the informed consent form should be signed and dated by the witness with the oral consent of the subject or his or her family, guardian, or legally acceptable representative.

If important new information about the investigational device or a clinical effect other than expected is found, the relevant contents of the informed consent form should be modified accordingly, and the modified informed consent form must be sent to the ethics committee for approval before it is signed by the subjects or their legally acceptable representative.

The informed consent form and process involved in this study have been prepared in accordance with the relevant requirements of the Good Clinical Practices for Medical Devices.

13、Definition of Adverse Events and Solutions

13.1 Definition of Adverse Events and solutions

Adverse Event (AE) refers to any untoward medical occurrence during treatment of subjects with the investigational medical device, whether or not considered related to the device.

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

Device related adverse events refer to complications related to the use of the investigational device, including deployment failure of stent and/or conversion to surgery, intra-operative bleeding, perforation or rupture of arterial wall, dissection or thrombus of access vessels, hematoma of the access vessels, pseudoaneurysm of the access vessels, infection of the access site, fever of unknown origin, aneurysm rupture, type I/III endoleak, stent migration, stent infection, limb stent-graft occlusion, pelvic or leg ischemia etc.

Any adverse events that occur during the study must be carefully recorded in the adverse event form. The investigators should provide targeted treatment for adverse events in accordance with local standards of care.

13.2 Definition of Serious Adverse Events and Solutions

Serious adverse events (SAEs) refer to events occur during the study that cause death or serious deterioration of health, including fatal illness or injury, permanent defect in physical structure or physical function, hospitalization or prolongation of hospital stay, necessity of medical or surgical intervention to avoid permanent defects in physical structure or physical function, or fetal distress, fetal death, or congenital anomalies/birth defects, and etc. In case of serious adverse events during the study, whether related to the study product or not, appropriate treatment measures must be taken immediately, and a written report shall be made to the appropriate department of the study site, and the sponsor shall be notified in writing as soon as reasonably possible. The appropriate department at the study site should report the matter in writing to the corresponding ethics committee,

and governmental Health Authority as appropriate and in accordance with local laws and applicable regulations, within 24 hours.

13.3 Definition of other adverse events related to the study

Heart related death: defined as death caused by arrhythmia, heart failure (including cardiogenic shock) or myocardial infarction.

Lung related death: defined as death due to pulmonary edema, respiratory failure, or pulmonary embolism.

Vascular related death: defined as death caused by stroke, intracerebral hemorrhage or other vascular events not classified as heart related or lung related.

Other deaths: Other deaths not clearly classified as described above.

All adverse events and serious adverse events should be reviewed by the principal investigator of the relevant site to determine the relevance of the device or surgery.

14、Deviation from and correction of study protocol

The study must be conducted in accordance with the study protocol approved by the relevant ethics committee.

Protocol deviations (PDs) will be categorized as follows: PD caused by investigator or study site and PD caused by subject non-compliance, both of which are sub-categorized as minor PD or major PD according to severity. Major PDs include but are not limited to violation of GCP principles, adversely affecting the safety and rights of subjects, adversely affecting the willingness of subjects to continue to participate in the study; adversely affecting data quality and integrity, inclusion of subjects who did not satisfy the inclusion criteria, inclusion of subjects who met the exclusion criteria, failure to review the primary endpoint and key secondary endpoints in accordance with the requirements of the protocol leading to a negative impact on the scientific integrity of the study.

Major PDs will be reported in the clinical summary report, while minor PDs will not be reported in the clinical summary report.

The investigators or the person appointed by the investigators shall record and explain any protocol deviation.

To immediately eliminate any harm to the subject, the investigator may take actions that deviate from the protocol without the prior consent of the ethics committee. The investigator shall report the protocol deviation, its reasons, and the proposal to amend the protocol (if applicable) to the ethics committee as soon as possible.

For any revision of the documents approved by the ethics committee that will not affect the rights and interests, safety and health of the subjects, or non-substantive changes not related to the study objectives or endpoint, prior notification to the study sites is not required, but written notice shall be given to them afterwards.

15、Source/Original data files

Source/original data files refers to the source records of clinical findings, observations and other activities in the study and all information in its approved copies, which can be used for reconstruction and evaluation of the study. Source documents refers to printed documents, visual documents, or electronic documents containing source data.

The source documents involved in this study include informed consent forms, subject screening and inclusion forms, subject identification code forms, subject SAE reports, subject medical documents, and study medical records. The case report form is not considered a source document in this study.

The subjects' medical documents include but are not limited to inpatient medical records, examination reports, films, and imaging records. Since there is no inpatient medical record in the outpatient / telephone follow-up after discharge, a study medical record for the recording of relevant information can be designed as a supplementary document to the inpatient medical record before the commencement of the study if deemed necessary.

16、Finance and insurance

See the clinical trial agreement signed by the sponsor and each study unit for details.

17、Clinical trial report

In accordance with the study protocol, each investigator shall contribute to the evaluation of the main study endpoint, discuss and compare the corresponding results of similar products, discuss verification of the safety and effectiveness of the device, and assist in completion of the clinical study report.

The clinical study report shall be issued by the lead study site.

The clinical trial report shall be consistent with the clinical trial plan, mainly including:

1. General information
2. Summary
3. Introduction
4. Study objective
5. Methods
6. Study content
7. Data summary
8. Study instruments
9. Statistical analysis method
10. Clinical evaluation criteria
11. Organizational structure
12. Ethical compliance statement
13. Results
14. Adverse events
15. Analysis and discussion of study results
16. Conclusion
17. Problems and suggestions for improvement
18. List of study personnel

The clinical study report shall be signed and dated by the Chief Investigator.

18、Confidentiality principle

All personal participant data is confidential, but it is possible that representatives of the relevant ethics committee, governmental departments, competent health authorities and the study sponsor may have reason to consult such data in specific circumstances. During the study, all parties shall abide by the principle of confidentiality and protect the privacy of subjects in clinical reports and published clinical data.

19、Study results publication agreement

The investigators shall not disclose the data or other information regarding the study to any third party for any purpose without the prior express written consent of the sponsor.

Without prior express consent, the sponsor shall not use the name of any investigator for commercial purposes including publicity and advertising of the study devices.

20、Responsibilities of parties

20.1Responsibilities of participating institutions and investigators

All study sites must be a clinical institution recognized by the local competent authorities with professional technicians and equipment suitable for undertaking the study, can supervise and organize the study, and provide representation at the relevant local independent ethics committee.

It should possess a dedicated department for the management of clinical trials, equipped with appropriate personnel, equipment, and facilities. It shall establish relevant working procedures and management systems for the training, quality supervision, adverse event handling and reporting of clinical trial related matters.

Before agreeing to participate in the study, the institution must evaluate the relevant resources according to the characteristics of the medical devices used for the study. It must undertake to keep clinical trial records and documents appropriately.

The investigators in charge of the clinical trial shall meet the following conditions:

1. Have corresponding professional and technical titles and qualifications in the study institution

2. Have the professional knowledge and experience required for the use of the investigational medical device and have received training if necessary

3. Be familiar with the data, literature and requirements related to study provided by the sponsor

4. Be able to coordinate, control and use the personnel and equipment for conducting the study, and can handle any adverse events and other related events relating to the study device

5. Be familiar with relevant national laws, regulations, Good Clinical Practice for Medical Devices, and relevant ethical considerations.

Prior to the initiation of the study, the investigators shall cooperate with the sponsor in applying to the relevant local ethics committee and submit the relevant documents as required.

The investigators shall ensure that relevant personnel receive training on the study device, including its indications for use, product performance, operation method, deployment requirements and technical indicators of the device, in order to understand the pre-clinical trial data and the safety profile of the device, and to understand the precautions and emergency treatment methods for any adverse events that may arise.

The investigators shall ensure that all relevant site personnel fully understand the protocol, the relevant regulations, and the characteristics of the study device, as well as their responsibilities related to the study, and ensure that enough subjects meeting the inclusion criteria of the protocol will be enrolled in the study. At the same time, they shall ensure that there is sufficient time to implement and complete the study in a compliant and safe manner within the period as agreed in the contract.

The investigators must strictly follow the study protocol, and in the absence of approval of the sponsor and the relevant ethics committee where appropriate, the investigators must not deviate from or materially change the protocol, unless in an emergency. However, the investigators should subsequently report the protocol deviation to the sponsor and the relevant ethics committee in written form as soon as possible.

The investigators are responsible for recruiting subjects and for informing the subjects of all relevant details of the study to enable participants to provide informed consent to participate in the study via completion of a signed and dated informed consent form.

The investigators or other persons involved in the study shall not force or unjustly influence the subjects to participate in or to continue with the study.

When an adverse event other than those expected for the study device occurs, the sponsor is required to modify the relevant contents of the informed consent form accordingly. Once the revised informed consent form has been submitted to and approved by the relevant ethics committee in accordance with relevant working procedures, the subjects must sign the revised informed consent form.

The investigators are responsible for ensuring that adequate and timely treatment and management are provided regarding adverse events. When a participant develops a disease or complication requiring treatment, the investigator should discuss this with the subject.

For all serious adverse events occurring during the study, including participant death, the study sites and investigators should immediately take appropriate treatment measures and report the incident to the relevant ethics committee and the sponsor in a prompt and detailed manner.

All adverse events occurring during the study must be documented by the investigators. The investigators should also analyze the cause of the events jointly with the sponsor, prepare a written analysis report, and where appropriate put forward suggestions for continuation, termination, or suspension of the study for the relevant ethics committee's consideration.

The investigators should ensure that study data is accurately, completely, clearly, and timely recorded in the Case Report Forms (CRF). The CRFs shall be signed by the investigator, and any change to the data recorded can be made only by the investigator; the amendment should be signed and dated, and the original record should be retained for comparison.

The study sites and the investigators have primary responsibility for the accuracy, clarity, and secure storage of study data, documents, and various records generated in the course of the study that are stored at the study site.

The study sites and the investigators shall allow inspection by the sponsor's monitoring personnel, as well as members of the relevant local ethics committee and/or government authorities, of all records related to the study as required for their review in accordance with the requirements of the monitoring personnel, the ethics committee, and the government.

If a risk related to the study is found to outweigh the potential benefits of the device's use, or the results of the study to date are insufficient to determine the safety and efficacy of the study device, and the study site and the investigator wish to terminate the study or suspend it, they shall notify the subjects, and ensure proper treatment and follow-up of the subjects; at the same time, the sponsor and the relevant ethics committee shall be notified immediately and a detailed written explanation for the termination or suspension of the study shall be provided. Where necessary, the government administration authorities shall be notified.

If a risk related to the study is found to outweigh the potential benefits of the device's use, or the results are study to date are insufficient to determine the safety and efficacy of the study device, and the sponsor or the ethics committee wish to terminate the study or suspend it, the investigators shall notify the subjects of the early termination or suspension of the study and ensure proper treatment and follow-up of the subjects continues in accordance with the relevant institution's standard of care.

Should the study be terminated by the local ethics committee, the study sites and investigators shall not restart the study without the consent of the ethics committee.

At the end of the study, the investigators should ensure that all records and reports are completed and archived as required. The relevant ethics committee and the sponsor shall be informed of this in a timely manner.

20.2Responsibilities of the sponsor

The sponsor is responsible for the initiation, application, organization, and monitoring of the study, and is responsible for the authenticity and reliability of its data. The sponsor is responsible for preparing and revising the study documentation, including the study protocol, the informed consent form, the case report forms, and other relevant documents.

The sponsor shall select the institutions and the investigators based on the characteristics of the study device and the study objectives. Prior to the signing of the clinical trial agreements with the study sites, the sponsor shall provide the sites and the investigators with the current version of the study documents for their consideration.

The sponsor shall not exaggerate the mechanism of action or the therapeutic efficacy of the study device when preparing the study protocol.

During the study, if new and important information becomes available to the sponsor, the sponsor shall revise the study documents if appropriate, submit them to the relevant ethics committee via the investigators for review, where appropriate, and provide them to all investigators after receiving approval from the relevant ethics committee where appropriate.

The sponsor shall agree the following in writing with all study sites and investigators:

1. The study shall be conducted according to relevant laws and regulations and study protocol.

2. Data recording/reporting procedure shall be followed.

3. Monitoring, verification and inspection shall be allowed.

4. The basic documents related to the study should be retained until the sponsor notifies the study sites and the investigators that the documents may be disposed of.

The sponsor shall establish the standard operating procedures related to the quality control of the study.

The sponsor is responsible for the safety of the study device during the clinical trial. Should any circumstance occur that is found likely to adversely affect the safety of the subjects, to affect the implementation of the study, or to change the approval of the ethics committee for continuation of the study, the sponsor shall immediately notify all relevant study sites and investigators and take appropriate actions.

The sponsor may terminate the clinical trial early or suspend it, provided that all study sites, investigators, and ethics committees shall be notified within one week of the decision of termination or suspension, and the reasons shall be set forth in writing. If the study is suspended, it shall not be restarted without the consent of the relevant ethics committees.

The sponsor should ensure that all the investigators conducting the study strictly follow the study protocol. If the sponsor finds that any site or investigator fails to follow the protocol, Good Clinical Practice for Medical Devices or the relevant regulations when conducting the study, the sponsor should notify the relevant investigator and site. If the deviation is deemed serious or is continued without correction; the sponsor shall consider whether the study should be terminated or suspended and should report the deviation to the local ethics committee and competent authorities where appropriate.

If the sponsor violates the relevant regulations or requests to modify the data and conclusion in circumstances other than in accordance with this protocol, the sites and the investigators may report the matter to the relevant local ethics committee and competent authorities where appropriate.

The sponsor shall assign a monitor for the study where necessary, and the responsibility for monitoring shall be borne by the sponsor.

The sponsor shall ensure the quality of the date collected in the study and, if necessary, inspect the implementation of the study protocol by assigning relevant personnel to and evaluate whether the study is being conducted in accordance with the requirements of the protocol, Good Clinical Practice for Medical Devices, and other relevant regulations.

The sponsor shall appoint the inspectors where necessary. Inspectors shall possess appropriate qualifications and have received relevant training. An inspection plan and inspection procedure may be created, depending on the the number of subjects, the type and complexity of the study, and its level of risk.

In case of serious adverse events, the sponsor shall report such events in accordance with this protocol to study sites, investigators, relevant local ethics committees and competent authorities where appropriate.

The sponsor should ensure that documents have been drafted prior to commencement of the study which clearly define the responsibilities of the Chief Investigator and other Principal Investigators.

The sponsor will promote communication between the investigators, formulate standard operating procedures in accordance with the study protocol, and cooperate with the Chief Investigator to carry out training on the protocol and the use of the study device for all the investigators participating in the study, to ensure the consistent application of the study protocol and use of the study device.

The sponsor should ensure that the design of the case report form is rigorous and reasonable, to enable the investigators to record all required data for the study.

21、 Signature of study sites, investigators and sponsor

Statement of Investigator:

I agree:

1. To carry out this study in strict accordance with the Declaration of Helsinki, the current local laws and regulations and the requirements of the study protocol.

2. To accurately record all required data in the Case Report Form (CRF) and assist in the drafting of the clinical trial summary report in a timely manner.

4. To allow the monitors and auditors authorized or dispatched by the sponsor and the regulatory authorities to conduct inspection, verification, and examination of the study as appropriate.

5. To strictly conform to the terms in the clinical trial agreement signed by both parties.

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

Sponsor:
Signature and date:

Investigator:
Signature and date:

Institution:
Signature and date: