Clinical Study Protocol for Medical Devices

A Retrospective Post-Market Clinical Study of the Flow Re-Direction Endoluminal Device System in the Treatment of Intracranial Aneurysms

Observational Device:	Flow Re-Direction Endoluminal Device System	
Model/Specification:	Refer to section 2.2.1 in this Protocol	
Management Category of Observational Device:	Class III Medical Device subject to clinical study approval	Yes☐ No ☒
	Similar product in China	Yes☒ No☐
Protocol Version and Date:	Version A, 2025-01-21	
Clinical Research Institution (Leading Institutions):	Henan Provincial People's Hospital	The First Affiliated Hospital of Zhengzhou University
Coordinating Investigator:	Tianxiao Li	Sheng Guan
Sponsor:	MicroVention. Inc	
Agent:	MicroVention (Beijing) Medical Technology Co., Ltd	

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List of Abbreviations

Abbreviation	Full Term
AE	Adverse Event
APTT	Activated Partial Thromboplastin Time
CEC	Clinical Event Committee
CI	Confidence Interval
CRA	Clinical Research Associates
CRO	Contract Research Organization
CTA	Computed Tomography Angiography
CS	Clinically Significant
CSR	Clinical Study Report
DSA	Digital Subtraction Angiography
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
FD	Flow Diverter
FIB	Fibrinogen
FRED	Flow Re-Direction Endoluminal Device
GCP	Good Clinical Practice
IA	Intracranial Aneurysms
ICF	Informed Consent Form
IFU	Instructions For Use
MRA	Magnetic Resonance Angiography
mRS	modified Rankin Scale
NMPA	National Medical Products Administration
OKM	O'Kelly-Marotta
PD	Protocol Deviation
PED	Pipeline Embolization Device
PI	Principal Investigator
PT	Prothrombin Time
SAE	Serious Adverse Event
SAH	Subarachnoid Hemorrhage
SAP	Statistical Analysis Plan
SAR	Statistical Analysis Report
SDV	Source Data Verification
TEG	thromboelastographic
TT	Thrombin Time
UIA	Unruptured Intracranial Aneurysms

Protocol Synopsis

Sponsor	MicroVention, Inc.
Study Title	A retrospective, post-market clinical study of the flow re-direction endoluminal device system in the treatment of intracranial aneurysms.
Protocol No.	CL1106094
Version/Date	Version A, 2025-01-21
Study Objective	To evaluate the long-term safety and efficacy of Flow Re-Direction Endoluminal Device System (FRED) in the treatment of intracranial aneurysms in the post-market environment
Study Design	Post-market, retrospective, multi-center, observational clinical study
Study Population	Patient who has implanted at least one observational device in China mainland.
Observational Device	Flow Re-Direction Endoluminal Device System (FRED)
Study Duration	About 36 months.
Inclusion and Exclusion Criteria	**Inclusion Criteria:** A patient is eligible for inclusion in the study if he/she meets all the following 1) People in China mainland who have been treated with FRED. **2)** The patients for whom clinical data are available. **Exclusion Criteria:** Patients who met the inclusion criteria at all time points were required to be included in the study. Therefore, no specific exclusion criteria were set.
Data Collection	**Demographic data and other baseline characteristics人口统计学数据和其他基线特征** • Birth date • Sex: Male/ Female • History of smoking and drinking: Yes/No • Ethnicity: Han/ another ethnicity • Diagnosis • Modified Rankin Scale (mRS) • Physical Examination: Neurological physical examination.

Medical History

- Past medical history: including current medical conditions (high blood pressure, diabetes, etc.), history of cranial and neurological related surgeries, hemorrhagic stroke.

Information of Procedure

- **Before Procedure**
  - Aneurysm Information: aneurysm location (left/right, C2 petrous segment - C7 terminus), aneurysm size (aneurysm maximum diameter, aneurysm neck, width, dome to neck ratio) and morphology (saccular aneurysm, dissecting aneurysm, fusiform aneurysm), ruptured / unruptured/ recurrent and the information of the parent artery (dimeter, stenosis) [Base Computed Tomography Angiography(CTA)].
  - laboratory examination (clinically significant abnormal results only).
  - Information of antiplatelet function test result: platelet aggregation test/ Thromboelastographic (TEG);
  - Information of anti-coagulation and anti-platelet medication: drug name, dosage and frequency of administration.
- **Using information of device**
  - Microcatheter: product name, model, size
  - Coil usage: Yes/No and number
  - Balloon: Yes/No and number
  - FRED: number, model, lot number
- **Information of procedure**
  - Puncture position (femoral artery/radial artery, left/right)
  - Re-sheathing performance: whether re-sheathing after release, re-sheathing times, re-sheathing success or not
  - Imaging results of immediate post-operation: stent fully cover the aneurysm neck, good wall apposition, parent artery perfusion, retention of contrast media.
  - Procedure complication: Complications of arterial puncture including pain, local bleeding, or injury to the artery, or adjacent nerves. Dissection or perforation of the parent artery, Rupture or perforation of the aneurysm, Vasospasm, Stent thrombosis, et al.
- **Information of follow up**
  - Imaging Evaluation of a Target Aneurysm: Digital Subtraction Angiography (DSA), Magnetic Resonance Angiography (MRA), CTA

	can be accepted. - Treatment-related hospitalization information or adverse event information: Stroke, Death, Adverse Event, Serious Adverse Event.
Endpoint	**Safety Endpoints[Adjudicated by Clinical Event Committee (CEC)]** 1) troke Rate 2) All-cause Mortality 3) Lesion-Related Symptoms or Signs Rate 4) Lesion-Related Complication Rate (Immediate post-procedure) 5) Adverse Event (AE), Serious Adverse Event (SAE)
	Efficacy Endpoints 1) Imaging Evaluation of Target Aneurysm [O'Kelly-Marotta(OKM) Grade] 2) Adequate Occlusion Rate of Target Aneurysm (Base Raymond-Roy Grade) 3) Technical Success rate (Immediate post-procedure) 4) Re-sheathing Performance (Immediate post-procedure) 5) Modified Rankin Scale (mRS) Change from Baseline
Statistical Analysis Method	**Sample Size Estimation** This study is an observational study that does not involve statistical hypotheses. Therefore, the plan is to collect data on as many patients as possible who received FRED treatment for intracranial aneurysms in China from May 2023 to May 2027, and as such, there is no specific sample size estimation. **Statistical Analysis Datasets** The dataset will consist of all study patients who meet the inclusion and exclusion criteria. **General Principles of Statistical Analysis** Detailed information on statistical analyses will be described in a separate Statistical Analysis Plan (SAP), with the final version of the SAP to be completed prior to database lock. The statistical analysis will be performed for this study using SAS® (version 9.4 or

	higher). This study is observational in design and does not involve statistical inference or hypothesis testing. Descriptive statistics for continuous variables will include the number of observations, mean, standard deviation, median, minimum, maximum values, and quartiles (Q1, Q3). **Baseline Analysis** Demographic, clinical characteristics, and treatment information of the patients including age, gender, medical history, physical examination, laboratory, surgical information, are statistically described. The methodology will adhere to standard principles. **Endpoint analyses:** This study is observational and does not involve statistical inference. Descriptive analyses will be conducted on safety and efficacy endpoints. For binary endpoints, counts and percentages will be provided, with 95% confidence intervals (CIs) estimated using the exact binomial method. Survival endpoints will be assessed using the Kaplan-Meier method to estimate survival probabilities and calculate the corresponding 95% CIs, accounting for censored data. Continuous endpoints will be summarized with counts, means, medians, standard deviations, minimums, maximums, and interquartile ranges, along with their 95% CIs. **Stage Analysis** According to the requirements of National Medical Products Administration (NMPA), the collected data will be divided according to the following schedule, and the statistics and analysis of clinical data during the corresponding collection period will be completed once a year: - During May 2023 to May 2025 - During June 2025 to May 2026 - During June 2026 to May 2027

1 Sponsor Information

1.1 Sponsor Name

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2 Clinical Study Background

2.1 Design Background

2.1.1 Disease Explanation

Intracranial Aneurysms (IAs) are abnormal bulges that caused by localized vascular wall damage in intracranial arteries. The prevalence of IAs in the general population is estimated to be approximately 3%-5%. Once an aneurysm ruptures, leading to Subarachnoid Hemorrhage (SAH), the mortality rate can reach up to 40%[1, 2].

The symptoms of IA can manifest as neurological dysfunction caused by mass effect or thrombosis, but the most common clinical presentation is SAH, typically presents with a sudden, severe headache and may be accompanied by transient loss of consciousness, vomiting, neck pain or stiffness[3]. Most Unruptured Intracranial Aneurysms (UIA) lack specific clinical symptoms and are often discovered incidentally, with only a few detected due to symptoms such as headaches or ptosis. Some patients with unruptured aneurysms may present with symptom, including visual disturbances (due to compression of the optic nerve), cranial nerve palsies (especially third nerve palsy), corticospinal tract dysfunction, and facial pains[4].

2.1.2 Treatment Options

The main principle of treating IAs is to exclude the aneurysm from the circulation to prevent rupture or re-rupture. There are two main treatment strategies: surgical clipping via craniotomy and endovascular treatment. The ideal endovascular treatment shall achieve complete aneurysm occlusion while preserving the parent artery. With this technique, a microcatheter is introduced via a transfemoral approach and manipulated into the cerebral aneurysm under fluoroscopic guidance. Following catheterization of the aneurysm, multiple detachable coils are placed within the aneurysm fundus, inducing aneurysm thrombosis, and again isolating the aneurysm fundus from the parent artery circulation[1].

Traditional endovascular techniques focus on intra-aneurysmal embolization, with primary methods including simple coil embolization and stent-assisted coiling. However, the effectiveness of these techniques is often constrained by the morphological characteristics of the aneurysm. Wide-neck aneurysms (defined as a neck width ≥ 4 mm or a dome-to-neck ratio < 2) are particularly challenging to treat. By utilizing coils for physical packing of the aneurysmal sac, the lack of effective support at the aneurysm neck often results in coil prolapse into the parent artery. This can lead to compromised blood flow to distal regions supplied by the parent artery, causing neurological deficits and severely affecting the patient's clinical outcomes.

Flow Diverter (FD) devices are developed based on reconstructing the parent artery’s lumen. FDs are designed with a denser mesh compared to conventional intracranial stents. By covering the aneurysm neck, these stents redirect blood flow away from the aneurysm, promoting intra-aneurysmal flow stagnation and subsequent thrombosis formation. Currently, FDs are primarily used for the treatment of wide-neck aneurysms[1].

At present, there are two major flow diverter devices in use. The first is the SILK, developed by BALT. The SILK device consists of a stent made from 48 braided nitinol and platinum alloy wires. The stent

delivery system comprises both the stent and a microcatheter, and the stent can be retrieved before 90% of deployment. SILK has been approved for marketing in the European Union. The second device is the Pipeline Embolization Device (PED), manufactured by Medtronic in the United States, which is similarly composed of 48 braided nitinol-platinum-iridium alloy wires. Its basic components are like those of the SILK device. PED has been approved for use in the EU, by the U.S. FDA, and by China's NMPA.

2.1.3 Observational Device

The design of the observational device Flow Re-Direction Endoluminal Device (FRED) system is comparable to other approved devices with the same or similar indications. FRED has been approved for use by the U.S. FDA on December 16, 2019, and received market approval from China's NMPA on May 12, 2022, with registration number 国械注进 20223130235. The self-expanding nitinol stent is the implantable portion of the Flow Re-Direction Endoluminal Device (FRED) system. The stent consists of two integrated nitinol braided inner and outer layers with the outer layer containing flare ends. The inner layer is of lower porosity, braided in a 36-wire format using 36 individual wires (FRED 2.5 mm and 3.0 mm), or 48 wire formats using 48 individual wires (FRED 3.5 mm to 5.5 mm). The outer stent layer is of higher porosity, braided in a 16-wire format using a single wire that is passed around a mandrel 16 times. Two radiopaque wires are inter-woven between the outer and inner layers along the length of the inner layer implant in a helix configuration. There are four radiopaque markers at each end of the stent.

The FRED system features a dual-layer stent design. The inner stent is similar in design to the SILK and PED devices, while the outer stent is designed with similar materials and structure to coil-assist stents currently in use, such as the LVIS™ (MicroVention), the Neuroform™ Stent System (Boston Scientific) and the Enterprise™ Vascular Reconstruction Device (Johnson & Johnson).

This clinical study is conducted in accordance with NMPA requirements to evaluate the long-term follow-up safety information of FRED following its market release.

2.2 Basic Composition of the Observational Device

2.2.1 Structural Composition

The FRED System [see **Figure 2-1** and **Figure 2-2**] consists of a self-expanding nickel-titanium implant and a delivery system. The implant is designed to expand to a pre-determined diameter when released from the delivery system. The implant features integrated dual layer coverage designed to focus mainly on the neck of an intracranial aneurysm. The implant has distal and proximal markers on its ends and interweaved helical marker strands delineating the inner working length of the implant to provide fluoroscopic visibility.

The FRED System is packaged sterile as a single unit with the implant, introducer sheath and a detachable delivery pusher. It is available in 7 different implant diameters ranging from 2.5 mm to 5.5 mm and in different implant lengths ranging from 13 mm to 45 mm. The FRED System 2.5 mm and 3.0 mm implants are compatible with the Headway 21 Microcatheter (FRED-21 System). The FRED System 3.5 mm to 5.5 mm implants are compatible with the Headway 27 Microcatheter (FRED-27 System).

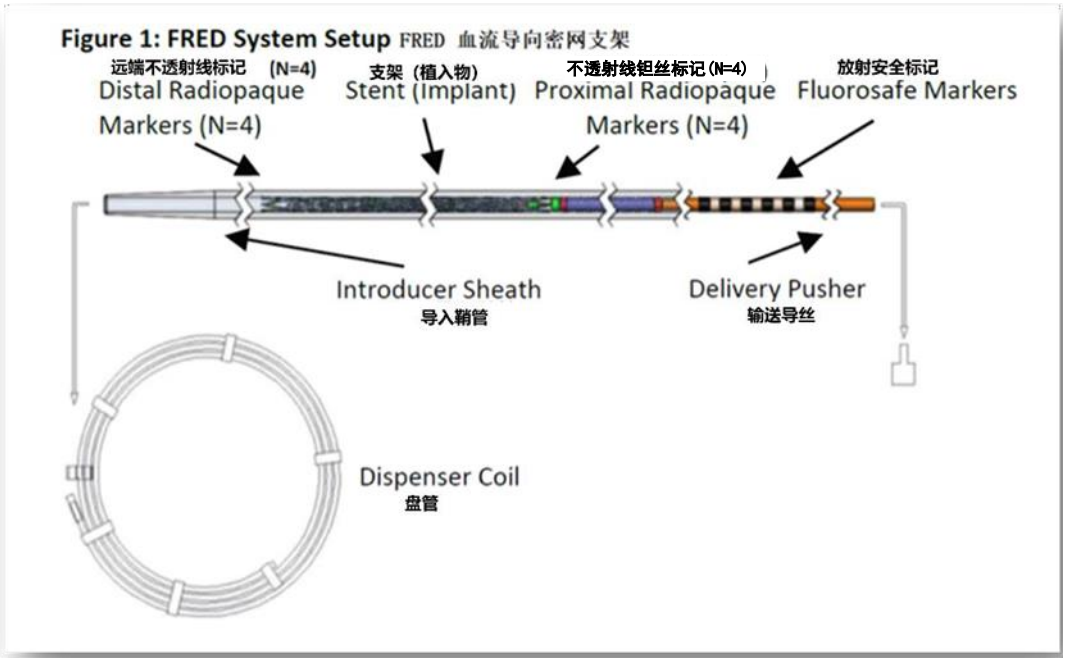

Figure 2-1 FRED System Setup

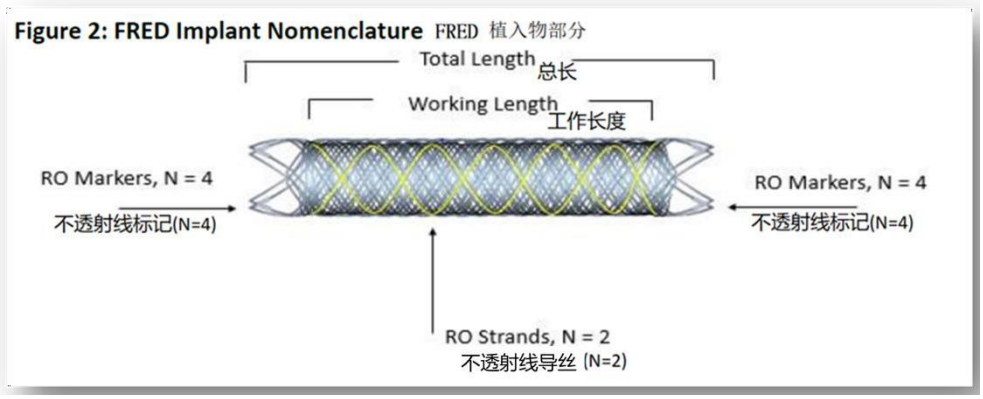

Figure 2-2 FRED Implant Nomenclature

Table2-1 List of Specifications and Models

Device	**Outer Diameter (mm)**	**Total Lengths (mm)**	**Working Lengths (mm)**
FRED System FRED	2.5	13~30	8~26
	3.0	13~32	9~27
	3.5	13、17、22、31、40	7、11、16、24、36
	4.0	13、18、23、32、44	7、12、17、26、38
	4.5	15、20、25、34、45	8、13、18、28、39
	5.0	15、21、26、36	9、14、19、29
	5.5	22、32	14、26
Specifications and Models of Product(s) to be Used in Combination			
Microcatheter	**Lengths**	**Minimum inner diameter of guide duct**	**Recommended Guide**
Headway 17	150 cm	0.056 inch / 1.42 mm	≤ 0.014 inch/ ≤ 0.36 mm
Headway 21	150 cm	0.056 inch / 1.42 mm	≤ 0.018 inch / ≤ 0.46 mm
Headway 27	150 cm	0.056 inch / 1.42 mm	≤ 0.018 inch / ≤ 0.46 mm

2.2.2 Principle of Operation and Mode of Action

The observation device is a flow diverter (FD) designed for permanent implantation into the lumen of the aneurysm or vascular dissection to carry the aneurysm. The approach site is usually an angiography-guided femoral artery. Neurovascular access is obtained according to standard endovascular maneuvers. This can be achieved by navigating the guidewire to the location of the aneurysm neck or to the target location, and then the microcatheter is navigated through the guidewire. After removing the guidewire, select the appropriate size flow guide according to the instructions for use (IFU). The instrument is assembled inside a coil and placed in a sterile area. The device (implant/delivery pusher/introduction sheath) is removed from the coil as a whole. The blood flow guide was inspected and prepared according to the IFU. Follow the "Instructions for Use" in the IFU to push the FRED implant into the microcatheter by pushing the delivery guidewire. By delivering a guidewire, the implant can advance further through the microcatheter until it reaches the distal tip of the microcatheter, but not beyond the microcatheter tip (proximal fluorescent labeling on the FRED delivery system can aid in this process). At this point, fluoroscopy must begin. While the implant remains within the microcatheter, it is positioned and deployed by aligning its distal radiopaque end marker. Once the position has been determined under fluoroscopy, the microcatheter is retracted and the delivery guidewire is advanced to allow the FRED implant to unfold in the aneurysm neck. If the implant is not fully deployed, it can be retracted and repositioned if necessary. Once deployed, the implant expands and clings to the wall of the blood vessel and across the neck of the aneurysm.

2.3 Scope of Application and Relevant Information

2.3.1 Indication(s)

The FRED System is indicated for use in the internal carotid artery from the petrous segment to the terminus for the endovascular treatment of adult patients (22 years of age or older) with wide-necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysms arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm.

2.3.2 Applicable Sites

Internal carotid artery from the petrous segment to the terminus.

2.3.3 Mode and Duration of Contact with Human Body

Prolonged and continuous blood contact (>30 days).

2.3.4 Applicable Disease Stage and Intensity

Intracranial aneurysms.

2.3.5 Condition of Use

Sterile medical environment.

2.3.6 Reuse

Sterile delivery, single use only.

2.3.7 Directions for Use

Please refer to Instructions for Use (IFU).

2.3.8 Contraindications

Use of the FRED System is contraindicated under these circumstances:

- Patients in whom anticoagulant, anti-platelet therapy, or thrombolytic drugs are contraindicated.
- Patients with known hypersensitivity to metal such as nickel-titanium and metal jewelry.
- Patients with anatomy that does not permit passage or deployment of the FRED System.
- Patients with an active bacterial infection.
- Patients with a pre-existing stent in place at the target aneurysm.
- Patients in whom the parent vessel size does not fall within the indicated range.
- Patients who have not received dual anti-platelet agents prior to the procedure.

2.3.9 Precautions and Warnings:

Please refer to Instructions for Use (IFU).

3 Clinical Study Objective

To evaluate the long-term safety and efficacy of post-marketing of Flow Re-Direction Endoluminal Device System (FRED) in the treatment of intracranial aneurysms.

4 Clinical Study Design

4.1 Overall Design and Selection Rationale

This is a post-market, retrospective, multi-center, observational clinical study.

The study plans to enroll patients who meet the eligibility criteria and have received at least one implantation of the observational device between May 2023 and May 2027. The retrospective data will be collected on baseline characteristics, information of procedure, and safety and efficacy endpoint to assess the safety and efficacy of FRED in the Chinese population. The efficacy endpoints include technical success rates and re-sheathing performance, the complete occlusion rate, and modified Rankin Scale (mRS) change from baseline. The safety endpoints include the rates of stroke, mortality, lesion-related symptoms or signs rate, lesion-related complication rate, adverse event, serious adverse event.

4.1.1 Number of Patients Required for Clinical Study and Rationale

No restrictions.

The eligible patients will be included between May 2023 and May 2027, without limiting the sample size of patients. This approach aligns with the NMPA requirements, which state, “Each product implanted in a patient shall be registered, and all patients implanted with the product shall be followed

up for a long time". By not imposing a limit on the number of enrolled patients, the study ensures that all eligible patients can participate, enabling a comprehensive assessment of the safety and efficacy of the FRED.

Moreover, this flexible recruitment strategy enhances sample diversity, allowing for a more accurate reflection of real-world clinical applications. A larger and more varied sample will facilitate a thorough analysis of outcomes across different patient demographics and conditions, ultimately strengthening the reliability of the study's findings and their applicability in clinical practice.

4.1.2 Expected Overall Duration of Clinical Study

About 36months.

4.2 Patient Selection

4.2.1 Inclusion Criteria

A patient is eligible for inclusion in the study if he/she meets all the following criteria:

1) People in China mainland who have been treated with FRED.

2) The patients for whom clinical data are available.

4.2.2 Exclusion Criteria

Patients who met the inclusion criteria at all time points were required to be included in the study. Therefore, no specific exclusion criteria were set.

4.3 Date Collection

4.3.1 Demographic data and other baseline characteristics

- Birth date
- Sex: Male/ female
- History of smoking and drinking: Yes/No
- Ethnicity: Han/ another ethnicity
- Diagnosis
- Physical Examination: Modified Rankin Scale (mRS), neurological physical examination.

4.3.2 Medical History

- Past medical history: including current medical conditions (high blood pressure, diabetes, etc.), History of cranial and neurological related surgeries, hemorrhagic stroke.

4.3.3 Information of Procedure

- **Before Procedure**

  - Aneurysm Information (Target): aneurysm location (left/right, C2 petrous segment-C7 terminus), aneurysm size (aneurysm maximum diameter, aneurysm neck width, dome to

neck ratio) and morphology (saccular aneurysm, dissecting aneurysm, fusiform aneurysm), ruptured / unruptured / recurrent and the diameter of the parent artery (Base CTA).

- Laboratory Examination(Clinically significant abnormal results only, that means abnormal laboratory test results that were judged by the investigator to be different from the normal standard values and had certain reference value for the diagnosis of clinical diseases).
- Information of Antiplatelet Function Test Result: platelet aggregation test/ thromboelastographic (TEG).
- Information of anti-coagulation and anti-platelet medication: drug name, dosage and frequency of administration are needed.

- **Using Information of Device**
  - Microcatheter: product name, model, size
  - Coil Usage: Yes/No and number
  - Balloon: Yes/No and number
  - FRED: number, model, lot number FRED：

- **Information of Procedure**
  - Puncture position (femoral artery/radial artery, left/right)
    Re-sheathing Performance: Whether re-sheathing after release, re-sheathing times, re-sheathing success or not
  - Imaging results of immediate post-operation: stent fully cover the aneurysm neck, good wall apposition, parent artery perfusion, retention of contrast media.
  - Procedure complication: Complications of arterial puncture including pain, local bleeding, or injury to the artery, or adjacent nerves. Dissection or perforation of the parent artery, Rupture or perforation of the aneurysm, Vasospasm, Stent thrombosis.

4.3.4 Information of follow up

- Imaging Evaluation of a Target Aneurysm: DSA、MRA、CTA can be accepted.
- Treatment-related hospitalization information or adverse event information: Stroke, Death, Adverse Event, Serious Adverse Event.

4.4 Endpoint

4.4.1 Safety Endpoint

(1) Stroke Rate

Definition: The stroke rate refers to the proportion of stroke patients in the total number of patients.
Collection Content: Record the date of stroke, type (ischemic or hemorrhagic), severity (mild, moderate, severe), location and cause, treatments, or other interventions for stroke, and whether the

stroke resulted in the patient's death. Also assess the relationship of the stroke event to the observational device and the patient's concurrent antithrombotic therapy. All stroke events are assessed by the CEC.

(2) All-cause Mortality

Definition: Mortality refers to the proportion of dead patients in the total number of patients.

Collection Content: Record the date of the death event and whether it was neurogenic. Evaluate the relationship of the death event to the observational device. Neurogenic death is defined as a death event directly resulted from a neurologic cause judged by the Clinical Event Committee (CEC).

(3) Lesion-Related Symptoms or Signs Rate

Definition: Lesion-related symptoms or signs rate refers to the proportion of patients with lesion-related symptoms or signs to total patients.

Collection Content: All neurological related symptoms which were not present at baseline or worsened from baseline will be record including headache, hemiplegic paralysis, seizure, aphasia, stroke, bleeding (including intracerebral, subarachnoid hemorrhage, retroperitoneal, others), facial nerve pain, seizures, vision loss, aphasia, hemiplegia, oculomotor nerve palsy, neck pain or stiffness, loss of consciousness, meningeal irritation, pre-retinal hemorrhage, increased intracranial pressure, other aneurysm-related symptoms, or abnormal signs (list specific symptoms or abnormal signs).

(4) Lesion-Related Complication Rate

Definition: Lesion-related complication refers to the proportion of patients with lesion-related complication to total patients.

Collection Content: Record whether the following complications occurred during the procedure. Principal Investigator (PI) shall evaluate the relationship between complications and observational device, other interventional devices, and surgical procedures.

- Complications of arterial puncture: including puncture site pain, puncture site local bleeding, injury to the puncture artery or adjacent nerves,;
- Dissection or perforation of the parent artery,
- Rupture or perforation of the aneurysm,
- Vasospasm;
- Stent thrombosis,
- Other complication

(5) Adverse Event, Serious Adverse Event (AE, SAE)

Definition: Refer to section 10 in this protocol.

Evaluation method: All Adverse Events (AEs) observed or reported will be assessed and recorded, and the causality and severity of AEs will be assessed according to the definitions and causality

assessment in Section 11 of this protocol.

The Principal Investigator (PI) shall assess whether an AE/ SAE meet the definition of surgical complication and safety collection index. If yes, the investigator shall complete corresponding surgical complication or safety evaluation indicator page.

4.4.2 Efficacy Endpoint

(1) Imaging Evaluation of a Target Aneurysm（O’ Kelly-Marotta,（OKM））

Definition: Based on the evaluation of imaging results, the treatment of aneurysms was classified according to the following criteria. Digital Subtraction Angiography (DSA), Magnetic Resonance Angiography (MRA), or Computed Tomography Angiography (CTA) are acceptable, and it is recommended base CTA. The purpose of imaging follow-up information collection is to observe the effect of on the long-term closure of the aneurysm after treatment. Complete closure of the aneurysm would be associated with increased safety.

- No filling
- Entry remnant (<5%)
- Subtotal filling (5%～95%)
- Total filling (>95%)

The observational device with the blood flow and the aneurysm gradually closes. The evaluation results of different follow-up nodes were counted, and the time interval between the date of surgery and the aneurysm occlusion is collected.

(2) Adequate Occlusion Rate of Target Aneurysm

Definition: Adequate Occlusion is defined as Raymond-Roy Grade I or Grade II on imaging evaluation of the target aneurysm [5]. If the Raymond-Roy grade reaches Grade I at any evaluation point, no further imaging information will be collected. Imaging results obtained via Digital Subtraction Angiography (DSA), Magnetic Resonance Angiography (MRA), or Computed Tomography Angiography (CTA) is acceptable. The imaging results will be evaluated following the routine procedures of the clinical research institution. The post-procedure recanalization of the aneurysm is graded according to the following classification. Please refer to **Error! Reference source not found.** for Raymond-Roy Classification Standards.

Table 4-1 Raymond-Roy Classification Standards

Grade	Description
Grade I	Complete occlusion (no contrast filling in the aneurysm sac or neck)
Grade II	Neck remnant (contrast filling in the aneurysm neck but not the sac)
Grade III	Residual sac (contrast filling in the aneurysm sac)

Occlusion Rate of Target Aneurysm refers to the proportion of patients judged to be Grade 1 or Grade 2 in the total number of patients.

(3) Technical Success Rate

Definition: Technical success is defined as successful stent placement and meet following criteria:

- Stent fully cover the aneurysm neck
- Good wall apposition
- Perfusion of the parent artery
- Retention of contrast agent within the aneurysm.
  The technical success rate refers to the proportion of technically successful patients in the total number of patients.

(4) Re-sheathing performance

Definition: During procedure, the observational device can be retrieved / re-sheathed into the microcatheter and re-deployed at the desired target location or removed completely from the patient. But it must not be re-deployed more than three times. Re-sheath performance refers to the retrieving and re-deploying of observational device recorded during the procedure. Information such as the number of recoveries and the number of re-sheathings, the success rate of re-opening and other information are recorded to evaluate the re-sheath performance of the observational device.

(5) Modified Rankin Scale (mRS) Change from Baseline

Definition: At different follow-up, the modified Rankin score changed from the baseline.

The modified Rankin (mRS) score was used to evaluate the improvement of neurological function. The modified Rankin score assesses the ability to live independently in patients with Neurological disease [6]. There are 7 levels of this score, 0 points represent no symptoms of disability, higher scores mean worse prognosis of patients, and 6 points represent death, See the table below for detailed scores.

Table 4-2 Modified Rankin Scale (mRS)

Score	Patient Condition
0	No symptoms of disability
1	Minor symptoms but no significant deficits; capable of all activities and work
2	Mild disability; unable to participate fully in previous activities but can live independently
3	Moderate disability; requires assistance but can walk independently
4	Moderate to severe disability; unable to walk independently, cannot live alone, requires some care
5	Severe disability; bedridden, incontinent, requires constant care
6	Death

4.4.3 Rationale for Evaluation Endpoints Selection

Rationale for safety endpoint selection: The safety indicators set for this study aligns with the NMPA requirements, which state, "The observation indicators include at least the following: ……, related stroke events, and clinical follow-up of deaths, strokes, and disease-related symptoms within 6 months". The recommendation of *Chinese guidelines for the treatment of intracranial aneurysms with flow divertor* is that the vast majority of occlusion of aneurysms after FD implantation occurs within 12 months after treatment. The incidence and severity of AEs/SAEs meet the relevant requirements for safety indicators in the *Guidelines for Clinical Study Design of Medical Devices*.

Rationale for efficacy endpoints selection: This clinical study is conducted in accordance with NMPA requirements to evaluate the long-term follow-up safety information of FRED following its market release. The efficacy indicators set for this study aligns with the NMPA requirements, which state, "The observation indicators include at least the following: technical success rate, re- sheathing performance, perioperative period". In addition, the observational device FRED features a finer mesh design compared to conventional intracranial stents, which allows it to cover the aneurysm neck, redirect blood flow, and promote blood stasis within the aneurysm, leading to thrombus formation and an increased aneurysm occlusion rate. To evaluate the efficacy of the observational device, the clinical study selected the aneurysm occlusion rate as the efficacy endpoint.

4.5 The Data Collection Schedule

The data collection schedule is described in

Table 4-3 Data Collection Plan

Baseline	Treatment*	Follow-Up Information**
• Demographic Information[1] • Medical History[2] • Physical Examination[3] • Imaging findings[4] • Modified Rankin Scale • Aneurysm Information[5] • Laboratory Examination[6] • Information of antiplatelet function test result: platelet aggregation test/ Thromboelastographic (TEG) • Information of anti-coagulation and anti-platelet medication[7]	• Using Information of Device • Information of Procedure • Stroke • Mortality • AE/SAE • O'Kelly-Marotta(OKM) Grade • Raymond-Roy Grade • Technical Success • Re-sheathing Performance	• Physical Examination[4] • Information of anti-coagulation and anti-platelet medication[7] • Image data • Lesion-Related Complication • Stroke • Mortality • AE/SAE [8] • O'Kelly-Marotta(OKM) Grade • Raymond-Roy grade • Modified Rankin Scale

Notes:
1. Demographic Information including: birth date, sex, history of smoking and drinking, ethnicity, diagnosis.
2. Medical History: Past medical history: including current medical conditions (high blood pressure, diabetes, etc.), history of cranial and neurological related surgeries, hemorrhagic stroke.
3. Physical Examination: neurological physical examination.
4. Image data collection, per standard of care (e.g., DSA, MRA, CTA) can be applied.
5. Based on CTA .
6. Laboratory Examination: Blood routine (red blood cell count, hemoglobin white blood cell count, neutrophil count, lymphocytes count, platelet count), coagulation test [Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Thrombin Time (TT) and Fibrinogen (FIB) International standardized ratio (INR)]. Only clinically significant abnormal results were recorded.
7. Information on anti-coagulation and anti-platelet medication: drug name, dosage and frequency of administration are needed.
*. If the same patient received other surgical treatments using observational device within the data collection time frame, only the first treatment data was selected as the baseline data, and the follow-up time was calculated at this point. The remaining surgical treatments were recorded as "concomitant surgery".
** Each patient may have multiple follow-up information, all of which should be recorded and collected. The collected follow-up data will be divided according to the following follow-up points: 30 days after surgery, 3 months after surgery, 6 months after surgery, and 1 year after surgery, according to the principle of closest approach.

4.6 Bias Control Measures

Multicenter Study: A multicenter design ensures that the case sample is more representative compared to a single-center study, thereby reducing the potential for bias caused by systemic errors

unique to a single center. This enhances the generalizability of the study results.

Standardized Data Collection: The eligible patients meeting the inclusion within the specified time frame, will be enrolled in this study to avoid selection bias. This ensures the integrity of the population under study and minimizes the risk of bias introduced by arbitrary patient selection.

Training of Data Recorders: Data collection personnel will undergo comprehensive training to ensure that all data are captured uniformly, in accordance with predefined data collection protocols and eCRF standards. Regular data audits and quality control procedures will be implemented to ensure the accuracy, reliability, and completeness of the data**.**

Data Review: Prior to database lock, a data review meeting will be initiated by the data management team. Attendees will include the principal investigator, the sponsor, data managers, clinical monitors, and biostatisticians. The primary objectives will be to finalize the statistical analysis dataset, evaluate any unreported AEs, verify any outstanding data queries, and decide on database lock and the formal approval of population stratification decisions.

Investigator Training: All investigators involved in this clinical study are highly experienced in the relevant therapeutic area. Prior to study initiation, Clinical Research Associates (CRAs) will conduct thorough protocol training sessions to ensure investigators are fully knowledgeable about the study design, endpoint definitions, and operational procedures. Investigators will rigorously adhere to the inclusion criteria and will document clinical data according to protocol-defined procedures.

Clinical Study Monitoring: Regular on-site monitoring visits will be conducted to ensure strict adherence to the study protocol. Source Data Verification (SDV) will be performed on eCRF to verify that the data recorded are consistent with the original source documents.

Identification of Confounding Variables: Potential confounders will be systematically identified. Any variable suspected to be a confounding factor, based on existing evidence, will be carefully documented. Factors that may influence both the intervention and the outcome will be thoroughly considered, and data collection will be as comprehensive as possible to ensure robust adjustment for confounding in the final analysis.

Clinical Events Committee: Medical data requested in the protocol will be provided to Clinical Events Committee under patient information protection for review. The personnel requirements of the CEC member and the contact details of the corresponding personnel will be recorded in a separate file. Evaluation and adjudication of safety endpoints as specified in the protocol will be completed by an independent Clinical Event Committee, and the relevant provisions for evaluation are referred to in the Clinical Event Committee bylaws.

5 Statistical Considerations

5.1 Sample Size Estimation

Not applicable.

This study is an observational study that does not involve statistical hypotheses. Therefore, the plan is to collect data on as many patients as possible who received FRED treatment for intracranial aneurysms in China from May 2023 to May 2027, and as such, there is no specific sample size

estimation.

5.2 Statistical Analysis Datasets

The dataset will consist of all study patients who meet the inclusion and exclusion criteria.

5.3 Statistical Analysis Methods

5.3.1 Statistical Analysis Plan

Detailed information on statistical analyses will be described in a separate Statistical Analysis Plan (SAP), with the final version of the SAP to be completed prior to database lock. Statistical analyses will be conducted according to the predefined SAP. Any changes to the statistical methods outlined in this protocol before database lock will be documented in SAP. Any modifications to the finalized SAP after database lock will be documented in the Statistical Analysis Report (SAR) and Clinical Study Report (CSR).

5.3.2 General Principle of Statistical Analysis

This study is observational in design and does not involve statistical inference or hypothesis testing. The statistical analysis will be performed for this study using SAS® (version 9.4 or higher).

Descriptive statistics for continuous variables will include the number of observations, mean, standard deviation, median, minimum, maximum values, and quartiles (Q1, Q3). Categorical variables will be described using frequencies and percentages. Unless otherwise specified, the significance level will be set at 5%, and the Confidence Interval (CI) will be set at 95%.

5.3.3 Baseline Analysis

The demographic, clinical characteristics, and treatment information of the patients were statistically described. The methodology will adhere to standard principles.

5.3.4 Endpoint analyses

Descriptive analyses will be conducted on safety and efficacy endpoints. For binary endpoints, counts and percentages will be provided, with 95% confidence intervals (CIs) estimated using the exact binomial method. Survival endpoints will be assessed using the Kaplan-Meier method to estimate survival probabilities and calculate the corresponding 95% CIs, accounting for censored data. Continuous endpoints will be summarized with counts, means, medians, standard deviations, minimums, maximums, and interquartile ranges, along with their 95% CIs.

5.4 Stage Analysis

According to the requirements of NMPA, the collected data will be divided according to the following schedule, and the statistics and analysis of clinical data during the corresponding collection period will be completed once a year:

- During May 2023 to May 2025
- During June 2025 to May 2026
- During June 2026 to May 2027

5.5 Management of Missing and Abnormal Values

Unless otherwise specified in a specific section, the missing values of baseline and safety data will not be filled.

For the missing efficacy endpoint, the missing values will be filled by the last carry-over method, the mean filling method or the multiple imputation method, and the specific filling rules and sensitivity analysis will be detailed in the statistical analysis plan.

5.6 Criteria for Eligible/Ineligible Clinical Study Results

This is a retrospective, multicenter, observational study, with both safety and efficacy assessments being descriptive analysis; therefore, no specific criteria for eligible criteria are set.

6 Data Management

6.1 Data Capture

Electronic Data Capture (EDC) will be used in this study, and clinical study data will be entered into eCRF by the investigators or authorized staff at the clinical research institutions. The investigators and authorized staff at the clinical research institutions will receive appropriate trainings before the initiation of clinical research institutions or data entering and appropriate measures will be adopted to protect the security of data.

The investigators will be responsible for maintaining all source documents and ensure they can be monitored by CRAs at each visit. In addition, the investigators shall submit a complete eCRF for every patient participating in the study, regardless of the duration of participation. The study number and patient number in all supporting documents (e.g., clinical research institution records) submitted with eCRF shall be checked carefully and all individual privacy (including the name of patient) shall be deleted, or measures shall be taken to make it difficult to identify patients to protect the privacy of patients.

6.2 Data Entering and Modification

The investigators or designers will be responsible for all entering, correction and modification of data. CRAs have no such permissions. All eCRF data will be submitted to the data manager. Any modification on data will be recorded by audit tracking, i.e., the reasons for modification, the name of the operator, time and date of the modification will be recorded. The role and permission of staff who are responsible for entering the data at the clinical research institution will be predetermined. CRAs or data management staff will raise queries in EDC for data and the staff at clinical research institution will be responsible for handling the queries. EDC system will record the audit tracking of queries, including the name of the investigator, time, and date.

6.3 Database Lock

The data manager, Principal Investigators (PIs), statistical analysis staff, sponsor and monitoring management staff will review the data together, complete the final definition and determination of population for analysis, and issue any necessary data queries. Then the database will be locked by data manager.

In general, locked database shall not be changed.

6.4 Database Transfer

The locked database will be transferred to statistical analysis staff for statistical analysis based on SAP.

7 Factors Influencing Study Success and Failure

7.1 Factors Influencing Study Success

The indications of the observational device is clear, and the composition and technical index are all in accordance with the related national and industry standards. This observational device, with clear principles and defined effects, complies with the applicable standards. At present, the devices used in this study have been approved and well used in China, and previous clinical studies have confirmed that they have good clinical effects and safety.

Before the start of the study, the clinical data records of each participating Institutions will be uniformly reviewed. The data records of the clinical research reference centers are standardized, the diagnosis and treatment records are complete, the data are traceable, and the original records are complete.

The study staff participating in the study have sufficient clinical experience and skilled operating ability. They also have sufficient patient resources, appropriate study teams, reasonable clinical study protocol, unified training for individuals participating in the study and unified recording procedure and standard of judgment. The investigators participating in the clinical study will be trained about the knowledge of the observational device and operating procedure by technicians of the observational device. The investigators shall follow the operating procedures strictly and all observations and laboratory results obtained during the clinical study shall be recorded and checked carefully to ensure authenticity and reliability of data and to ensure that all conclusions in the clinical study are based on source data.

7.2 Factors Influencing Study Failure

The non-compliance of study conducts with protocol, incomplete records of observations and laboratory test results during the clinical study, or lack of source data supporting may cause the failure of this study, but these factors are controllable.

Each patient participating in the clinical study will be clinically followed up comprehensively. The medical records of each patient will be fully monitored to observe the occurrence of complications closely and create detailed emergency treatment regimen. Regularly review the patient's medical records and record AE information in detail.

In conclusion, the probability of success for this clinical study is high, with a low likelihood of failure. However, the potential for failure is correlated with operational risks, patient-related factors, and the underlying disease characteristics.

8 Quality Control of Clinical Study

8.1 Investigator Training

(1) Organize training related to the clinical study of the observational device and participate in the clinical study of the medical device within the scope authorized by the principal investigator; (2) Fully understand and comply with clinical study protocols and relevant laws and regulations and responsibilities related to clinical research of observational device.

8.2 Data Management

All data inputs are in Chinese. eCRF shall be completed during or as soon as possible after each visit and updated at any time to reflect patient status updates. The data shall be reviewed by the investigators to ensure the accuracy and authenticity of all data entered the eCRF. If any evaluation is not performed during the trial or any information is unavailable, inapplicable, or unknown, the investigators shall record it in the eCRF. The investigators shall electronically sign the verified data.

8.3 Setting Clinical Events Committee

The Clinical Events Committee (CEC) is a group of independent experts, who is responsible for reviewing and adjudicating adverse events in the study, to ensure that the judgment of adverse events in clinical research meets the requirements of the protocol.

The CEC committee will be composed of independent clinical experts with experience or expertise in neurosurgery, and who are not involved in this study. The CEC will provide the definition and evaluation criteria of the adverse events in accordance with the CEC charter and this protocol, and review and adjudicate the specific events reported.

9 Ethical Considerations and Informed Consent of Clinical Study

9.1 Ethical Considerations

The clinical study must be conducted in accordance with the *Declaration of Helsinki*, and appropriate regulations and laws. The clinical study protocol shall be approved by the ethics committee (EC) of the leading site before conducting the study.

The investigators need to submit the protocol, ICF (If any), and other related documents through the management department of the clinical research institution to the EC before the initiation of the study. The clinical study will be conducted after approved by the EC. Any modification on the protocol shall be approved by the EC before implementation.

Clinical research institutions for medical devices shall meticulously maintain clinical research records and foundational documents in compliance with applicable laws and regulations.

9.2 Patient Inform Consent Process

This study is a retrospective study and does not involve the informed consent of patients, and an ICF waiver will be applied to the ethics committee. If necessary, an informed consent process will be performed as required by the Ethics Committee.

10 Adverse Event, Serious Adverse Event

10.1 Adverse Event

10.1.1 Definition

An Adverse Event (AE) is any untoward medical occurrence during the clinical study, whether or not related to observational devices (from *Good Clinical Practice for Medical Devices*).

10.1.2 Determination of Severity

According to following criteria, severity of AEs can be categorized as mild, moderate, and severe.

- Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- Moderate: Marked limitation in activity, assistance usually required; medical intervention / therapy required, possible hospitalization.
- Severe: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or probable hospice care.

10.1.3 Determination of Causality Relationship Between AEs and Devices AE

The causality relationship of AEs with medical devices included "definitely related", "possibly related", "likely unrelated" and "definitely unrelated". "Definitely related" and "possibly related" are judged as related to the observational device; "likely unrelated" and "definitely unrelated" are judged as unrelated to the observational device. The specific judgment criteria are as follows:

Related to the observational device: (1) There is a reasonable temporal relationship between the AE and the observational device; (2) The AE is consistent with the known hazard of the device or may be explained by the mechanism of the observational device; (3) The harm is alleviated or disappears after the use of the device is stopped; (4) The harm occurs again after the use of the device is resumed; (5) The AE cannot be explained by other reasons. It is judged as "definitely related" if all five criteria are met and as "possibly related" if two of them are met.

Unrelated to the observational device: (1) There is no reasonable temporal relationship between the AE and the observational device; (2) The AE is a type of event that is unlikely to be caused by the observational device; (3) The AE can be explained by concomitant device(s)/drugs, patient disease progression, and other therapeutic effects. It is judged as "definitely unrelated" if all three criteria are met and as "likely unrelated" if one of them is met.

The severity of adverse events and their relevance to devices or procedures will be determined independently by the CEC Committee in accordance with the unified regulations and principles, combined with the collection data (the collection data collection includes patient medical records, laboratory tests, and, if necessary, patient's imaging data.) to make a judgment.

10.1.4 Reporting and Follow-up

The investigators shall record all AEs that occur during the study, including the name, start and end

dates, severity, causality relationship with the device, and outcome of each AE, as well as any action taken for each AE.

The investigators shall provide symptomatic treatment and follow-up for each AE until all symptoms disappear or become stable, or otherwise there is another reasonable explanation.

10.2 Serious Adverse Event

10.2.1 Definition

A Serious Adverse Event (SAE) refers to any AE occurrence during a clinical study that causes any of the following situations:

- death; or
- serious deterioration in the health of the patient, including:
  - a life-threatening illness or injury; or
  - a permanent impairment of a body structure or a body function; or
  - involved or prolonged inpatient hospitalization;
  - medical or surgical intervention to prevent permanent impairment to a body structure or a body function;
- fetal distress, fetal death or congenital abnormality or birth defect.
- Other medically significant events.

All definition above comes from *Good Clinical Practice for Medical Devices*.

Note: Planned hospitalization for a pre-existing condition or a procedure required by the clinical investigation plan, without serious deterioration in health is not considered an SAE.

10.2.2 Reporting of SAEs

For SAEs, investigators shall conduct a comprehensive analysis and assessment of the SAE immediately after becoming aware of it, including its severity and relationship to the observational device. For suspected SAE related with medical device, investigators shall report to relevant personnel. For SAEs lead to death or SAEs lead to serious injury, reports must be submitted within reported within the prescribed time frame.

11 Clinical Event Committee

The Independent Clinical Event Committee (CEC) will evaluate safety endpoints data and the sponsor will appoint a CEC composed of physicians (not investigators) to rule uniformly adjudicate all SAE and/or AEs associated with the observational device or observational procedure identified. Only CEC's determinations of the collected data (Data collection includes patient medical records, laboratory tests, and, if necessary, patients' imaging data) were used for the analysis of safety endpoints.

12 Protocol Amendments

If there is any modification to the protocol after EC approval, a “protocol revision statement" or revised protocol is required, which shall be signed and confirmed by the sponsor and the coordinating investigator and approved by the EC before implementation.

13 Direct Access to Source Data and Documentation

Source data refers to the original records of clinical findings, observations, and other activities in a medical device clinical study, as well as all information in certified copies, which can be used for the reconstruction and evaluation of the clinical study.

Source documents refer to printed documents, visual files, or electronic files that contain source data.

The archived materials for this clinical study include: (1) clinical study protocol; (2) electronic case report forms (eCRFs); (3) informed consent forms (If any); (4) original medical records of the patients; (5) statistical analysis reports; (6) all other materials such as interim reports and final summary reports of the clinical study.

Investigators must carefully complete all study documents, including the confirmation of all participated patients (effectively verifying different records, such as eCRFs and original hospital records), all original signed informed consent forms of patients (if any), and detailed records in all eCRFs. After the study is completed, all clinical study documents shall be submitted to the clinical research institution for safekeeping.

14 Clinical Study Report

The contents of a clinical study report for a medical device clinical study shall include its general information, conduct, statistical analysis methods, study results, reports of AEs and their handling, analysis and discussion of study results, clinical study conclusions, ethical description, finding, and suggestions for improvement.

15 Principle of Confidentiality

The protocol is confidential, which is provided to related medical experts, related personnel such as investigators participating in the study, and authorized agencies for related operations such as medical institutions undertaking this study, ECs and Contract Research Organization (CRO). Besides explaining situation to patients, any content of this protocol shall not become public or be disclosed to a third party without a prior written agreement from the sponsor. In addition, if any part of or all results of this clinical study are going to be published in external media such as societies and journals, written approval from the sponsor shall be obtained.

The contents of this clinical study and all the attached materials are confidential, exclusive to the sponsor, and investigators shall be responsible for the confidentiality. No confidential information, including patent application, manufacture process and unpublished data that the sponsor provides investigators, shall be disclosed to any third party unless being agreed by the sponsor, and the confidentiality obligation remains valid after termination or end of this study.

Investigators and their staff will collect patients' personal data being used in this study ("study data"), including date of birth, gender, identity card, home address, photos and physical or mental health data.

All medical records and research materials that can identify patients will be kept confidential within the scope of law. However, the management departments of clinical research institutions, ECs, drug regulatory authorities, healthcare administrative departments or monitors, auditors are allowed to review the personal data o patients participating in the clinical study as necessary to perform their work in accordance with the prescribed procedures. All personal information in the study will be handled in accordance with the national and local data protection laws.

Patients have the right to request investigators and sponsor to protect their information and to correct any inaccurate information in such data. If patients withdraw informed consent, investigators will no longer use or disclose their data, and sponsor may still use the data acquired before withdrawing.

The study results may be published in medical journals and presented at medical conferences. Patients will not be identified in any of these publications.

16 Responsibilities of All Parties

16.1 Responsibilities of Sponsor

(1) The sponsor of a medical device clinical study shall establish a quality management system covering the entire process of the clinical study to ensure that the study complies with relevant laws and regulations, and to protect the rights and safety of patients.

(2) Prior to the start of the medical device clinical study, the sponsor shall submit the required documents to the EC through the Principal Investigator.

(3) The sponsor is responsible for the authenticity and compliance of the medical device clinical study. If the sponsor is a foreign entity, it must designate a domestic legal entity in China as its agent in accordance with relevant laws and regulations, and the agent shall assist the sponsor in fulfilling its responsibilities.

(4) The sponsor shall sign contracts with the medical device clinical research institution and the principal investigator, clearly defining the rights and obligations of all parties involved in the clinical study.

(5) Before the start of the medical device clinical study, the sponsor is responsible for organizing training related to the study, such as on the clinical study protocol, SOPs, and other relevant documents.

(6) To ensure the quality of the clinical study, the sponsor may organize audits conducted by auditors who are independent of the clinical study and have the necessary training and experience, to assess whether the study is being conducted in accordance with the study protocol and relevant laws and regulations.

(7) The sponsor shall ensure that the clinical study is conducted in compliance with the clinical study protocol. If the sponsor discovers that the clinical research institution or investigator is not adhering to the protocol or relevant laws and regulations, it must promptly identify the issue and correct it. If the non-compliance is serious or persists, the sponsor shall terminate the participation of the institution and investigator in the study.

(8) The sponsor shall have the necessary facilities and conditions for storing essential clinical study documents and shall establish a document management system. The essential documents of the medical device clinical study shall be divided into three parts based on the study phase: preparatory phase documents, in-progress phase documents, and post-completion or termination documents.

(9) The sponsor and the medical device clinical research institution shall ensure the integrity of essential clinical study documents during the storage period, preventing intentional or unintentional alterations or loss. The sponsor shall retain the essential documents until the medical device is no longer in use.

16.2 Responsibilities of Medical Device Clinical Research Institutions

(1) The medical device clinical research institution shall establish a quality management system that covers the entire process of conducting the clinical study, to ensures that the principal investigator fulfills their research-related responsibilities, provides proper medical care to patients, and ensures the authenticity of the data generated from the study.

(2) Before accepting a medical device clinical study, the clinical research institution shall assess relevant resources based on the characteristics of the observational device, ensuring that it has the appropriate qualifications, personnel, facilities, and conditions.

(3) The medical device clinical research institution and investigators shall cooperate with monitoring and auditing organized by the sponsor, as well as inspections conducted by drug regulatory and health administration departments.

(4) The medical device clinical research institution shall properly maintain clinical study records and essential documents in accordance with relevant laws and regulations, as well as the contract with the sponsor.

(5) The medical device clinical research institution shall have the necessary facilities and conditions for storing essential documents and shall establish a management system for these documents. The essential documents shall be divided into three parts based on the study phase: preparatory phase documents, in-progress phase documents, and post-completion or termination documents.

(6) The medical device clinical research institution shall ensure the integrity of essential documents during the storage period, preventing intentional or unintentional alterations or loss.

16.3 Responsibilities of Investigators

(1) Develop clinical study protocols, sign clinical study protocols, and be familiar with the use of observational device.

(2) According to the needs of clinical study of medical devices, the principal investigator authorizes investigators who have undergone relevant training in clinical study to organize data collection and collation; the management and use of observational device; management and use of biological samples (as applicable); management of adverse events; recording of clinical study data and filling in case report forms, etc.

(3) When adverse events are found in clinical study, the investigator shall record adverse events that occur during the clinical study.

(4) The investigator shall complete the analysis, judgment, and reporting of serious adverse events in accordance with relevant laws and regulations.

(5) The principal investigator shall report to the ethics committee on the progress of the clinical study of medical devices on time.

17 Miscellaneous Issues to be Clarified

17.1 Finance and Insurance

In this clinical study, the sponsor will sign a written agreement with the clinical research institution, which will detail the financial arrangements, insurance, and payment methods for the study. The specific details are outlined in the agreement signed by the parties involved.

17.2 Agreement on Study Result Publication

The sponsor and the investigators shall agree on the final clinical study report. Results of this clinical study may be published as scientific literature or submitted to authorities. The following provisions are made to protect trade secret materials: All information about the observational device (e.g., patent application, unpublished manufacture processes, basic scientific data provided to the investigators by the sponsor) is considered confidential and proprietary to the sponsor. Investigators are not allowed to use it for other purposes without written permission from the sponsor. If the investigator plans to reveal or publish study result, the manuscript should be provided to the sponsor 90 days before the reveal study result or paper publication, and the sponsor shall review the manuscript and make comments within the 90 days, according to generally accepted principle of collaboration in scientific fields, investigators shall discuss and agree on publications with the sponsor's personnel prior to publication.

Investigator Statement

I agree:

1. To conduct this clinical study in strict compliance with the *Declaration of Helsinki*, *Good Clinical Practice (GCP)* (2022), current regulations in China, and the clinical study protocol.
2. To accurately record all required data in eCRF and complete the clinical study report on time.
3. To allow the CRAs and auditors authorized or dispatched by the sponsor and regulatory agencies to monitor, review, and inspect this clinical study.
4. To strictly perform the terms of clinical study contracts/agreements executed by all parties.

I have thoroughly read the clinical study protocol, including the statement above, and I agree with all the above.

Opinions of Principal Investigator Signature:： _____ Date:： _____ (DDMMMYYYY)

Opinions of Sponsor (seal) Date: _____ (DDMMMYYYY)

Opinions of Medical Device Clinical research institution (seal) Date: _____ (DDMMMYYYY)

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