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Program number: JQR001

Efficacy and safety of a neurointerventional operation robotic assistance system in cerebral angiography

Name of investigational medical device: minimally invasive vascular interventional surgical assistance system

Model specification: YDHB-NS01

Management categories of investigational medical devices:

three categories

Class III medical devices subject to clinical trial approval: Yes☐ No☑

Similar products in China: Yes☐ None☑

Scheme version number and date: V3 0/20210915

Clinical trial institution: Beijing Chaoyang Hospital affiliated to Capital Medical University

Coordinator: Wang Yang

Sponsor: Yidu Hebei Robot Technology Co., Ltd

Agent: Feiwei (Shanghai) Pharmaceutical Technology Co., Lt

Sponsor information

(1) Name of sponsor: Yidu Hebei Robot Technology Co., Ltd

(2) Address of the sponsor: 1st floor, Block B, Building 2, Baoding Zhongguancun Innovation Base, No. 369 Huiyang Street, Baoding City

(3) Contact information of the sponsor: Chen Yang 0312-5905155

(4) Relevant qualification documents of the sponsor: see Annex

(5) The agent's name, address, contact information, and relevant qualification documents

Name of agent: FINWAY (Shanghai) Pharmaceutical Technology Co., Ltd

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Relevant qualifications: see annex

A list of all clinical trial institutions and investigators

Code	Clinical trial institution	Researcher	Title	Contact
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Purpose and content of clinical trials

objective

This study is a pre-marketing clinical trial of minimally invasive vascular interventional surgical assistance system, which provides clinical data for the formal application of the product in China by evaluating the effectiveness and safety of minimally invasive vascular interventional surgical auxiliary system in cerebrovascular interventional angiography Basis.

content

1. Clinical study evaluation endpoints

1. Main evaluation indicators

success rate.

2. Secondary evaluation indicators

Operation time.

2. Effectiveness evaluation methods

1. Validity:

Definition of successful angiography: The catheter arrives at the location to enable successful imaging of the target vessel.

Definition of operating time: the time from the entry of the catheter into the body to the withdrawal of the catheter.

2. Performance indicators:

Operator evaluation: whether the operation station is stable, whether the catheter and guide wire delivery are smooth, whether the support robotic arm is flexible, whether the controller is flexible, and whether the equipment fails.

3. Safety evaluation methods

1) The amount of radiation from the X-rays of the patient subject.

2) Incidence rate of complications: intraoperative and 3 days after surgery (if the discharge time is ahead, that is, at the time of discharge). Observe and record the occurrence and timing of complications in patients who were followed up with the trial.

Complications include:

1. Puncture-related: perivascular hematoma puncture, vasospasm at the puncture site, vascular

dissection, pseudoaneurysm, arteriovenous fistula, puncture site infection.

2. Procedure-related: intracranial vasospasm, atherosclerotic plaque sloughing, thrombosis, vascular injury, vascular dissection, vascular perforation, vascular rupture, vascular occlusion, pseudoaneurysm, arteriovenous fistula, hemorrhage, intracranial aneurysm or arteriovenous malformation, air embolism.
3. Neurological complications: transient ischemic attack, epilepsy, opisthotonistolus, complete amnesia, ischemic stroke.
4. Contrast agent-related: allergy, nausea, vomiting, cerebral edema.

3) Adverse events

Adverse events include but are not limited to: Major Adverse Cardiovascular Events (MACE): defined as vascular dissection, vascular avulsion, vascular rupture, new cerebral embolism, bloodstream infection, and death. Cortical blindness, broken guidewire, kink, severe allergy to contrast media, lung infection, renal failure, impaired consciousness, death, malfunction of robot operation.

Background

According to the World Health Organization, about 17.9 million people died of cardiovascular and cerebrovascular diseases in 2016, accounting for 31% of the total deaths, of which 85% died of heart disease and stroke [1]. According to the "China Cardiovascular Disease Report 2017", there are about 290 million patients with cardiovascular and cerebrovascular diseases in China, including 270 million patients with hypertension, 13 million patients with stroke and 110 million patients with coronary heart disease [2]. Cardiovascular and cerebrovascular diseases accounted for 45.01% of the deaths of residents' diseases, 45.01% in rural areas and 42.61% in urban areas, ranking first among various diseases, higher than tumors and other diseases [2-3].

At present, the treatment of cardiovascular and cerebrovascular diseases is divided into drug therapy and surgical treatment, and there are usually two methods of surgical treatment, one is traditional open surgery, and the other is minimally invasive vascular interventional surgery [4]. Traditional open surgery mainly uses open cavities or craniotomy to expose the location of the lesion and then treat. This method has great tissue damage to the patient, a large amount of bleeding, slow postoperative recovery, high risk of surgery, and the patient needs to bear great pain [5,6]. Compared

with traditional open surgery, minimally invasive interventional surgery makes an incision at the blood vessel, and under the guidance of medical imaging, special medical catheters and guidewires are inserted from the incision and pushed to the lesion location, and then other medical devices are used to treat the lesion location, such as the dissolution of thrombus, the placement of vascular stents, etc. [5,7]. The use of interventional surgery for treatment has the advantages of less trauma, less bleeding, fast postoperative recovery, reduced pain, and fewer complications, and has been widely used [5]. During interventional procedures performed on the spot, doctors need to use X-rays to complete the entire operation. To avoid the harm caused by radiation, doctors often wear bulky lead clothing. Due to the limited protective area of lead clothing and the need for doctors to work under radiation for a long time, doctors have an increased risk of cancer [8]. During the operation that lasts for several hours, doctors need to wear lead clothing weighing up to 10 kg, which is very easy to cause fatigue and easily induce chronic diseases such as cervical spondylosis and lumbar spondylosis [9]. The specialized vascular interventional robot technology provides an effective solution to the above problems, which can promote the further development and wide application of traditional vascular interventional technology.

The minimally invasive vascular interventional surgery assistance system aims to combine robot technology with traditional vascular interventional technology, and use the rapidity, high stability, high positioning accuracy, high computing power and rich sensing information of robots to realize the expansion and extension of doctors' capabilities and solve the problems and limitations of traditional vascular interventional surgery. Most vascular interventional surgery robots adopt master-slave control mode, which is composed of the doctor-to-master-end console, slave-end robot, image interaction system and control system. During robot-assisted surgery, the doctor adopts a sitting posture in front of the console, controls the specially designed operation handle or button, realizes the control of the slave robot, and the slave robot realizes the pushing, pulling and twisting operation of the catheter, so as to reproduce the doctor's surgical operation, and at the same time detects the operating force of the catheter from the internal sensing system of the end robot and sends it to the main console in real time, and the feedback force generation device of the main end console provides the doctor with tactile feedback of the operating force of the catheter. During the operation, the doctor observes the surgical status of the catheter in the human vascular lumen through the image interaction system (DSA, MRI and other medical images), and makes surgical operation decisions based on the tactile feedback of the hand, so as to complete the vascular interventional operation.

This product has passed the test of Beijing Medical Device Inspection Institute of the State Medical Products Administration, and the performance indicators have met the standard requirements, and the test results are qualified.

This product has been tested on animals to verify its safety and efficacy in animals. According to the relevant content of the "Good Clinical Trial Practice for Medical Devices" (Order No. 25 of the State Food and Drug Administration), clinical trials were conducted to verify their clinical safety and effectiveness.

Product characteristics, structural composition, working principle, mechanism of action and test range

1. Product features

The main features of the minimally invasive vascular interventional surgical assistance system are as follows:

(1) The system adopts master-slave operation mode. The system slave operator is set on the patient side and the main end operator is set on the doctor side, and the master-slave control can use both wired communication set in the same city and network communication mode set up in different places. When wired communication is used, the main operator (doctor's side) is located in the close isolation area outside the operating room, freeing the doctor from the radiation working environment. When using network communication, the main manipulator (doctor's side) can be set in a remote place far away from the patient (operating room), which can effectively extend the doctor's skills, expand the coverage of surgery, and reduce the geographical dependence of complex surgery on experts.

(2) The system slave operator can provide at least 2 degrees of freedom catheter operation movement. In the process of vascular interventional surgery, the movement of the catheter relative to the vascular incision has forward or backward axial movement, and the rotational movement around the catheter itself, and the operation of the catheter needs to provide at least 2 degrees of freedom under the premise of meeting the requirements of surgical operation. In most studies, robotic systems typically provide 2 degrees of freedom operation because the catheter has only linear and rotational motion relative to the blood vessel. In some studies, the catheter was modified to increase the control of the catheter head rotation, improve the operability of the catheter, and enhance the catheter's ability to

cross vascular branches. Because this method increases the size of the catheter to a certain extent, it is generally only suitable for cardiac surgery.

(3) The design form of the main end operator of the system is diversified. The function of the master operator of the system is to collect the operation movements of the doctor's hand and transmit the signal to the slave operator to control the catheter. According to the difference in the configuration of the main end operator and the slave end manipulator, it is divided into homogeneous and heterogeneous type. The main end operator using the homogeneous design method, its structure and motion form are the same as the slave operator, the advantage of this design method is that the control of the master and slave system is simple and convenient. The main end operator adopts heterogeneous operation mode, which designs a special operation handle according to the specific surgical operation requirements, such as the different operation methods of cerebrovascular interventional surgery and abdominal interventional surgery, which is convenient for doctors to operate. In heterogeneous master-side operators, in order to increase the comfort of the doctor's operation, redundant degrees of freedom are usually set, so the degrees of freedom of the master-side operator are often greater than those of the slave-end operator.

(4) The system adopts different signal feedback methods to assist doctors in surgical operations. There are two main kinds of motion signals: position signal and collision signal, the former reflects the running posture of the catheter guidewire in the blood vessel, and the latter characterizes the collision relationship between the catheter guidewire and the blood vessel wall. At present, the minimally invasive vascular interventional surgery auxiliary system adopts signal feedback methods, including visual feedback and force feedback. However, most studies used visual feedback to assist physicians, and some introduced force feedback. The combination of visual feedback and force feedback can reproduce the motion information of the catheter guidewire more comprehensively and increase the safety of surgery.

2. Product structure composition, working principle, mechanism of action

1）Structural composition

The minimally invasive vascular interventional surgical assistance system consists of the following components:

- Doctor console

-Robot body - support manipulator - catheter controller - guide wire controller - auxiliary support tube

-Electrical control box - chassis frame - connection cable

- Computer - Control software system

2）Working principle and mechanism of action

This system is used to assist doctors to complete catheter and guidewire delivery operations in vascular interventional surgery. The operator uses the doctor's console and computer workstation to complete the robot action control. The robot body and support robotic arm are fixed on the operating table and move together with the operating table, and the catheter controller, guide wire controller and auxiliary support tube are installed in the corresponding card slots of the robot body, and the delivery operation of the catheter and guide wire is carried out according to the operation instructions.

The catheter manipulator and guide wire manipulator can realize the independent back and forth movement of the conduit and guide wire and rotate around the self-axis.

The doctor's console is used for remote control catheter controller, guidewire controller, output catheter, and guidewire delivery action. The doctor's console includes controls for catheter and guidewire delivery control. During the operation, the catheter and guidewire manipulator on the robot side are synchronized with the controller action. When the handle corresponding to the catheter operator pushes forward and pushes back, the catheter controller pushes forward and withdraws the catheter at a fixed speed; When the handle is twisted clockwise or counterclockwise, the catheter controller synchronizes the rotation of the catheter. When the handle corresponding to the guide wire operator pushes forward and backward, the guide wire controller pushes forward and retreats the guide wire at a fixed speed; When the handle is twisted clockwise or counterclockwise, the guidewire controller synchronizes the rotation of the guidewire. The robotic body catheter and guidewire manipulator use a linear propulsion method to drive the catheter and guidewire into or out of the blood vessel. The catheter manipulator remains tightly attached to the catheter and does not undergo axial relative displacement during the procedure. The guidewire manipulator adopts a reciprocating delivery operation, and the axial delivery operation of the guidewire is carried out by "manipulator clamping-delivery-manipulator relaxation-gripper retraction" during the operation.

3. Scope of the research

This study is a pre-marketing clinical trial of minimally invasive vascular interventional surgical assistance system, which evaluates the safety and efficacy of minimally invasive vascular interventional surgical auxiliary system in cerebrovascular interventional angiography by comparing it with conventional cerebrovascular interventional angiography and provides a clinical basis for the formal application of the product in China.

Indications and contraindications of the product, possible complications and precautions

1. Indications

Cerebrovascular lesions or conditions suspected to be cerebrovascular related and requiring cerebral angiography, including, but not limited to: intracranial aneurysm, cerebrovascular malformations, cerebrovascular stenosis, cerebral arteriovenous fistula.

2. contraindication

The surface material of this product is ABS plastic, which is sensitive to the material of the surface parts of this product.

3. Possible complications and precautions

Including but not limited to: vascular dissection, vascular avulsion, vascular rupture, new cerebral embolism, blood infection and death.

4. Precautions and warnings

4.1 warn

- Do not disassemble or modify all parts and systems of this instrument by yourself.
- This product should only be operated by a professional technician who is familiar with interventional surgery and trained in the use of this robotic system.
- Please use this product for surgical operation with fluoroscopy display.
- When using this product, please choose the guide tube and guide wire that are suitable for the model.
- The non-disposable part of this product is not sterile storage, and the instrument needs to be cleaned and disinfected with alcohol cotton before each use.

- When using this product, please try to avoid strong electromagnetic field interference. The use of mobile phones or mobile RF communication devices in the vicinity of this product may interfere with the normal operation of the equipment.

4.2 Precautions

- This product must be trained before use and qualified before surgical operation.
- The catheter manipulator and guide wire manipulator in this product should use the type of instrument identified at the time of purchase, and do not use non-suitable type instruments.
- As shown in Appendix B, please follow the electromagnetic compatibility instructions for this product.
- Do not use this product outside the operating room.
- This product should be cleaned after each use, as detailed in the training manual.
- This product should be routinely maintained after 100 surgical procedures.
- If any component of the system still does not function after you have tried all the recommended troubleshooting methods, contact your product provider immediately.
- Do not discard this product at will, contact the equipment manufacturer for recycling.
- If you want to obtain the paper random file of this device again, please call the after-sales service and verify the user information and obtain the document by email.

Overall design

1. experimental design

1）Purpose of the test

This study is a pre-marketing clinical trial of minimally invasive vascular interventional surgical assistance system, which evaluates the effectiveness and safety of minimally invasive vascular interventional surgical assistance system in cerebrovascular interventional angiography by comparing it with conventional cerebrovascular interventional angiography to provide a clinical basis for the formal application of the product in China.

2）Choice of test method and its rationale

This was a randomized, parallel, controlled, non-inferior multicenter clinical study. Conventional cerebrovascular interventional angiography was used as a positive control. The success rate of imaging

was used as the primary endpoint index; The incidence of clinical complications, adverse events and performance indicators 3 days after contrast surgery (if the discharge time is before, that is, at the time of discharge) were used as safety evaluation indicators. To evaluate the efficacy and safety of the test group.

3）Measures to reduce and avoid bias

Due to the characteristics of the medical device itself, it is difficult to achieve double blinding, so bias can only be controlled from the following aspects

1. The operation standards used by the experimental group and the control group were the same: the participants in the trial were required to receive product operation training, each center was operated by two or more doctors with more than intermediate titles, and each center was required to complete the same number of experimental and control subjects.
2. Loss to follow-up: Take corresponding measures in the study, record the details of the subjects, and try to obtain the cooperation of the study subjects to obtain the highest possible response rate, reduce the non-response rate, loss to follow-up and dropout in the trial study, etc.
3. Randomization: The randomization method was used to control the enrollment bias, scraping the silver area covered by the random card in the order of patient enrollment, and the subjects were divided into groups and treated accordingly according to the prompt information on the random card.
4. Main index evaluation: Contrast imaging data are evaluated by third-party experts.

4）Experimental medical devices and control medical devices

4.1 Comparison of experimental medical devices with control medical devices

Investigational medical device: minimally invasive vascular interventional surgical assistance system

Model specification: YDHB-NS01

Manufacturer: Yidu Hebei Robot Technology Co., Ltd

Control medical devices: select conventional cerebral vascular interventional contrast in clinical practice

4.2 Instrument preservation

Operating conditions

- Room temperature: 10 °C to 40 °C
- Relative humidity: 30% to 75%.
- Atmospheric pressure: 700 to 1060 hPa

Transportation and storage conditions

- Current room temperature: -20 °C to +60 °C
- Relative humidity: 10% to 90%.
- Atmospheric pressure: 500 to 1060 hPa

5）Subject selection

1) Inclusion criteria

- Patients are between 18-7and 5 years old, regardless of gender.
- cerebrovascular patients requiring interventional angiography.
- Participants voluntarily signed informed consent.

2) Exclusion criteria

- Severe infectious diseases, severe coagulation dysfunction, serious heart, brain, lung and other diseases.
- Those who are allergic to control contrast agents.
- severe hepatic and renal disease.
- Pregnant and lactating women and those planning to become pregnant within one year.
- Those who have participated in clinical trials of any drug and/or medical device within 3 months prior to enrollment.
- The investigators believe that there are any other factors that are not suitable for inclusion or affect participants' participation in the study.

3) Dropout criteria**:**

Dropout cases refer to cases that have signed informed consent and been screened into the trial, but for some reason have not completed the entire process of clinical trials. Cases of exfoliation should be included in FAS analysis. When the patient falls out, the investigator must fill in the reason for the dropout in the eCRF form and complete as many evaluation items as possible. Cases of exfoliation due

to adverse events must be recorded in the CRF and should be included in the adverse event evaluation. Patients who shed out cannot be replaced. Common causes of shedding are:

- loss to follow-up.
- Due to adverse events, especially serious adverse events, subjects, principal investigators, ethics committees, supervisors or/and heads of clinical pharmacology bases, national or local drug administrations in charge consider terminating the study from an ethical point of view.
- Selected subjects went against the trial protocol.

4) Exit Criteria

- Those who have allergic reactions or serious adverse events and should stop the test according to the doctor's judgment.
- Those whose condition deteriorates during the test and should stop the test according to the doctor's judgment.
- Investigators judged participants with poor adherence.
- Participants withdrew on their own.
- For whatever reason, the subject is unwilling or unable to continue the clinical trial and terminates the trial by requesting the investigator to withdraw from the trial.
- Participants were no longer accepted for follow-up although they did not explicitly withdraw from the trial.

5) Suspension criteria

- If a serious safety incident occurs during the test, the test should be stopped in time;
- If a major error is found in the clinical trial protocol during the trial, or although the plan can be implemented, there is a serious deviation in the implementation, and it is difficult to evaluate the efficacy of the product, the trial should be discontinued;
- If the product is found to have poor therapeutic effect or device defects in the test and has no clinical value, the test should be discontinued;
- The sponsor requests that the test be suspended;
- The administrative department revoked the test.

6) Time of enrollment, expected overall duration of clinical trials and reasons for their determination

This clinical trial is planned to be carried out in 6 research units of Beijing Chaoyang Hospital affiliated to Capital Medical University, Shanxi Provincial People's Hospital, the First Affiliated

Hospital of Zhengzhou University, Yangtze River Shipping General Hospital, the First Hospital of Hebei Medical University, and the Affiliated Hospital of Hebei University, and the clinical trial enrollment time is expected to be about 2 months, and time is also required for ethical meetings, data collation and statistics, and writing clinical trial summary reports, so the overall time of clinical trials is about 8 months.

7) The expected duration of participation for each subject

Each participant completed the trial 3 days after contrast (i.e. at discharge if the discharge time was ahead), so the duration of each participant's expected participation in this clinical trial is approximately 1 week.

8) Number of subjects required for clinical trials

In this trial, 260 subjects (130 in the experimental group and 130 in the control group) will be screened, and the enrollment will be completed by 6 hospitals: Beijing Chaoyang Hospital Affiliated to Capital Medical University, Shanxi Provincial People's Hospital, The First Affiliated Hospital of Zhengzhou University, Yangtze River Shipping General Hospital, First Hospital of Hebei Medical University, and Affiliated Hospital of Hebei University.

6) Effectiveness evaluation method:

6.1 Validity:

Definition of successful angiography: The catheter arrives at the location to enable successful imaging of the target vessel.

Definition of operating time: the time from the entry of the catheter into the body to the withdrawal of the catheter.

6.2 Performance indicators:

Operator evaluation: whether the operation station is stable, whether the catheter and guide wire delivery are smooth, whether the support robotic arm is flexible, whether the controller is flexible, and whether the equipment fails

7) Safety evaluation method

7.1 The amount of radiation on X-rays of the patient subject.

7.2 Incidence of complications: intraoperative and 3 days after surgery (if the discharge time is ahead, that is, at the time of discharge). Observe and record the occurrence and timing of complications in

patients who were followed up with the trial.

Complications include:

- Puncture-related: perivascular hematoma puncture, vasospasm at the puncture site, vascular dissection, pseudoaneurysm, arteriovenous fistula, puncture site infection;
- Procedure-related: intracranial vasospasm, atherosclerotic plaque sloughing, thrombosis, vascular injury, vascular dissection, vascular perforation, vascular rupture, vascular occlusion, pseudoaneurysm, arteriovenous fistula, hemorrhage, intracranial aneurysm or arteriovenous malformation, air embolism;
- Neurological complications: transient ischemic attack, epilepsy, opisthotonistolus, complete amnesia, ischemic stroke;
- Contrast agent-related: allergy, nausea, vomiting, cerebral edema;

7.3 Adverse events

Adverse events include but are not limited to: Major cardiovascular adverse events (MACE): defined as vascular dissection, vascular avulsion, vascular rupture, new cerebral embolism, bloodstream infection, and death. Cortical blindness, broken guidewire, kink, severe allergy to contrast media, lung infection, renal failure, impaired consciousness, death, malfunction of robot operation.

8）Clinical study evaluation endpoints

8.1 Main evaluation indicators:

Success rate.

8.2 Secondary evaluation indicators:

Operation time.

9) Demographic and baseline indicators

- Demographic characteristics: record the age, sex, height, and weight of each subject.
- Vital signs: record body temperature, heart rate, blood pressure, breathing.

2. Process

（1）Experiment flowchart

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Visiting period	**Enrollment**	**Cerebral angiography**	**Postoperatively**
Number of visits	**V1**	**V2**	**V3** If the discharge time is first, that is, at the time of discharge
Days	**-7~1 day**	**1 day**	**1~3 days**
informed consent	X		
Demographic characteristics	X		
Present and past medical history	X		
Vital signs	X	X	X
Review inclusion and exclusion criteria	X		
Randomization	X		
Angiographic recording		X	
Pregnancy test[0]	X		
Blood routine[1]	X		
Coagulation function[2]	X		
Liver function, kidney function[3]	X		
electrocardiogram	X		
Combined medications	X	X	X
complication		X	X
Adverse events/serious adverse events		X	X
Performance evaluation		X	
Instrument defects		X	

0 Pregnancy test: performed during the screening period for women of gestational age.

1Blood count: hemoglobin (HGB), red blood cell count (RBC), platelet count (PLT), white blood cell count (WBC) 。

2 coagulation function: prothrombin time (PT), fibrinogen (FIB), activated partial thromboplastin time (APTT), thrombin time (TT).

3 liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), alkaline phosphatase (ALP), glutamyltransferase (GGT), renal function: blood urea (UREA), blood creatinine (CR) 。

The above laboratory tests can be accepted within one week before screening.

Statistics

The statistical analysis will be processed using SAS 9.4 or later statistical analysis software, all statistical tests will use a two-sided test, and a P-value less than or equal to 0.05 will be considered statistically significant for the difference tested. (Unless otherwise stated).

The description of the quantitative indicator will calculate the number of cases, mean, standard deviation, median, minimum, maximum. The classification indicators are described using the number and percentage of each category.

For the comparison of the general conditions of the two groups, the group-based t-test or Wilcoxon rank sum test was used for the comparison of quantitative indicators, the chi-square test or exact probability method (if the chi-square test was not applicable) was used for classification indicators, and the Wilcoxon rank sum test or CMH test was used for grade data.

Data management

In this study, EDC was used for the collection and management of research data, and the system was provided by Gemast (Beijing) Information Technology Co., Ltd. The system is a computer network-based data collection platform, for clinical trial data collection, data transmission and data management, the system has timely data entry, real-time data challenge, data audit track, data verification, data verification, electronic signature, data locking, data storage and export and other functions, support internationally recognized data standards (such as CDISC standards). The application of this system ensures the quality of clinical trial data and its true integrity. The entire data management process is implemented in accordance with national laws and regulations and relevant data management SOPs. The main processes of data management are listed below, and other details are described in the Data Management Plan (DMP). The DMP is written by the Data Manager (DM) as a guiding document for data management, approved by the sponsor, and the data management work will be carried out according to the time, content and method defined by the DMP.

Data management workflow diagram

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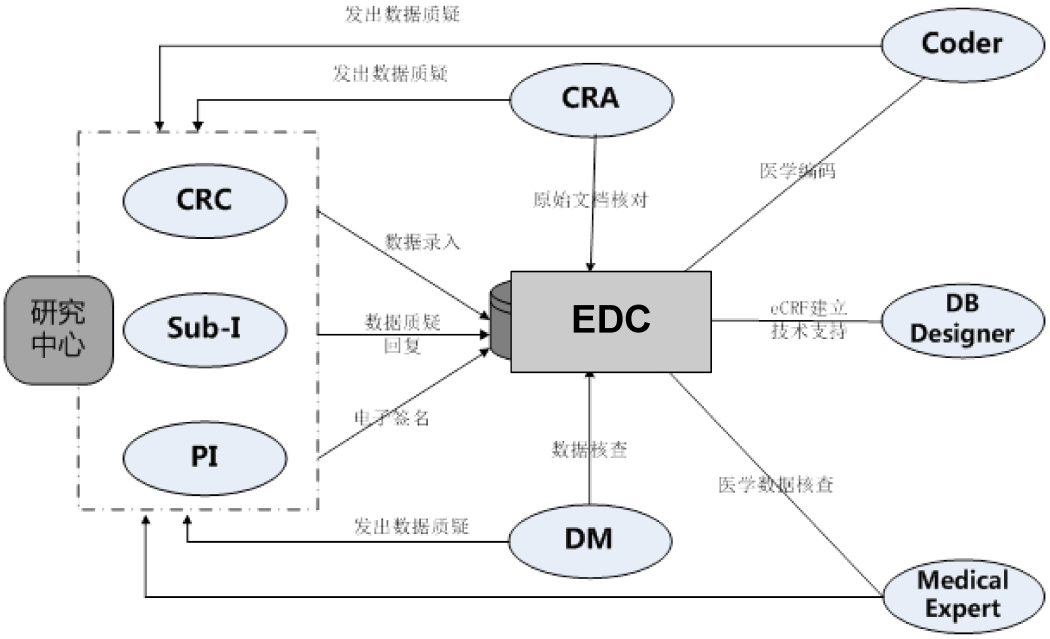

Feasibility analysis

1. Analysis of the likelihood of success

This product has passed the State Food and Drug Administration Beijing Medical Device Inspection Institute testing, all performance indicators have met the standard requirements, and through animal tests to verify the safety of the product in animals to reduce the risk in clinical trials.

Subjects are selected by experienced physicians in strict accordance with clinical trial protocols and a thorough assessment of their condition.

2. Analysis of the likelihood of failure

If the conclusion based on the statistical results is that the complications of the experimental group are higher than those in the control group, or serious adverse reactions occur, it means that the safety of this product is poor, and it is not suitable for clinical use. The efficacy of the experimental group is worse than that of the control group, and it is statistically significant, indicating that the efficacy of this product is not accurate, and the efficacy remains to be evaluated by other trials, and it is not suitable for clinical practice.

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Quality control of clinical trials

During a clinical trial, it is important to ensure that appropriate quality control measures are in place throughout the clinical trial process. Take the following specific quality control measures:

1. Standard Operating Procedure (SOP) training

Conduct unified SOP training for all researchers, be familiar with the specific implementation rules and operating procedures of clinical trial protocols and standardize recording methods and judgment standards. During the trial process, researchers must carefully implement the clinical plan, and the factors and indicators that have an important impact on the test results (including inclusion criteria, exclusion criteria, treatment plan, primary efficacy indicators, secondary efficacy indicators, safety indicators, dropout rate, etc.) should be controlled in key areas, and the contents of the case report form should be truthfully, carefully and carefully recorded according to the requirements of the case report form when filling in the case report form to ensure that the content of the case report form is complete, true and reliable.

2. Clinical monitoring

Establish independent clinical monitors, who will formulate monitoring plans, lists and question forms, and regularly conduct on-site monitoring visits to clinical trial institutions according to the progress of enrollment to ensure that all contents of the research protocol are strictly observed and the correct and complete filling in of research materials. The contents of the audit include:

- Check and trace all trial data on a case-by-case basis, check the completeness, authenticity and timeliness of the data records in the case report form, and track and verify the report of adverse events (AE);
- All factors and indicators that have an important impact on the trial results (including inclusion criteria, exclusion criteria, treatment regimens, primary evaluation endpoints, secondary evaluation endpoints, safety indicators, dropout rate, etc.) should be verified and confirmed on site;
- The clinical monitor must provide corresponding monitoring records and reports for each monitoring and submit them to the investigator;
- For problems found in the audit, a question form must be drawn up and submitted to the researcher for verification and confirmation before making changes.

Liu H, *et al. Stroke Vasc Neurol* 2023;0:1–9. doi: 10.1136/svn-2022-002260

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Ethical and informed consent for clinical trials

1. Ethics

It is the investigator's responsibility to provide the ethics committee with copies of the clinical trial protocol, detailed patient information page, and informed consent form to obtain independent approval documents for the conduct of the clinical trial.

Approval documents from the ethics committee must be obtained before the start of the clinical trial. The approval document of the ethics committee must be sent to the investigator in writing, with the list of members attending the meeting, professional information and signatures, and then the researcher will provide a copy of the approval document to the sponsor.

During clinical trials, any issues related to the safety of clinical trials, such as changes to clinical trial protocols or patient information pages, and serious adverse events in clinical trials, must be reported to the ethics committee in a timely manner. The end or early termination of a clinical trial must also be reported to the ethics committee.

2. Approval of test protocols

The design, conduct and reporting of this trial are in accordance with the Good Clinical Practice for Medical Devices, the Declaration of Helsinki (2013), and the relevant regulations and ethics committee opinions of the National Medical Products Administration (NMPA).

Before the trial begins, the investigator/research unit should obtain written approval from the ethics committee on the trial protocol, informed consent form, case report form, and other written information to be provided to the subject. During the trial, if there are any new revisions to the trial protocol, informed consent, etc., they should be approved or filed in writing by an independent ethics committee again.

3. The informed consent process and the text of the informed consent form

The investigator or his/her designated representative will be responsible for informing each subject of the research background, characteristics of the test medical device, the test protocol, and the benefits and risks of participating in the trial, and shall obtain written informed consent signed by the subject or his/her legal representative and the study physician before the subject enters the trial (prior to screening examination). The procedure specified in the programme can only be commenced if a signed

informed consent has been obtained.

Investigators will be provided with a sample informed consent form that is individually applicable to the study and reviewed by the ethics committee in accordance with GCP and regulatory requirements. The final informed consent text should contain the following: the purpose of the trial, the procedure of the test, the subject's obligations, the foreseeable benefits of participation in the trial, and the foreseeable risks and inconveniences; treatment and appropriate compensation available to subjects in the event of trial-related damages; Access to trial data and confidentiality of subject information, etc.

The informed consent form is described in a language that the subject can read. Participants and their representatives performing the informed consent process must sign and date the informed consent form. The original informed consent form should be retained by the investigator and the subject with one copy each. If there is important new information involving investigational medical devices, the informed consent form must be amended in writing, sent to the ethics committee for approval, and the subject's consent must be obtained again.

Women of childbearing age should be informed that they may have unknown risks to the fetus if they become pregnant during the study; If they wish to participate in this study, contraceptive requirements should be observed during the study; If participants are suspected of not complying with these contraceptive requirements, they cannot participate in this study.

The process of obtaining informed consent should be documented in the subject's original documentation.

Regulations for reporting adverse events and device defects

1. Definition of adverse events

Adverse events are adverse medical events that occur during clinical trials, whether or not device-related.

Adverse events included the following:

- All suspected adverse device effects;
- the presence of obvious non-related disorders, i.e., symptoms or diseases that were not present at the time of study entry;
- The deterioration of a pre-existing condition, that is, the simultaneous appearance of some

symptoms or diseases. Pre-existing conditions mean that some disease or symptom was present before the study began, and there is an original record on the medical history/physical examination record prior to treatment;

- accidental injuries or accidents;
- Any improper and unanticipated event for a medical device is an undesirable device effect, i.e., it is related to the use of the investigational product. Any adverse events caused by improper instructions for the use of the device, as well as any adverse events due to the user's error, are included in this definition.

2. Criteria for determining the severity of adverse events

- mild: perceptible signs or symptoms that do not require discontinuation of the device and special treatment;
- moderate: symptoms and signs are tolerable, require special treatment, do not interfere with daily life;
- Severe: symptoms and signs are intolerable, requiring discontinuation of the device and special treatment, affecting daily life.

Note: Adverse event severity is used to describe the intensity of the event, not necessarily the adverse event.

3.Criteria for judging the causal relationship between adverse events and medical devices

- Affirmatively related: the use of instruments and the timing of reaction occurrence are reasonable; After stopping the use of the device, the reaction stops, or rapidly relieves or improves; With reuse, the reaction reproduces and may be significantly aggravated; At the same time, there is documentary evidence; and have ruled out the influence of other confounding factors such as the original disease;
- It is likely to be related: no history of repeated use of the device, Yu Tong "definite", or although there is a combination of other devices or drugs, the possibility of a reaction caused by the combination of other devices or drugs can be basically excluded;
- May be related: the use of instruments is closely related to the time of reaction, and is supported by literature; However, more than one device or drug that causes adverse reactions, or the progression factors of the underlying disease cannot be excluded;
- May not be related: adverse reactions are not closely correlated with the time of use of the

device, the reaction manifestations are not consistent with the known adverse reactions of the device, and the development of the original disease may also have similar clinical manifestations;

- Unrelated: The occurrence of the reaction is not significantly related to the chronological order of device use; inconsistent with the type of adverse reactions of the device; The patient's clinical state or other causes may also explain the reaction, and the response is reduced or eliminated after clinical symptoms or other causes are excluded.

4.Outcome determination of adverse events

Adverse events outcomes include:

- Death: leading to the end of life (the cause and time of death must be collected);
- Unhealed/not relieved: AE has not improved/recovered after treatment;
- Recovery: After treatment of AE, the symptoms completely disappeared without sequelae;
- Sequelae: After treatment of AE, the symptoms have disappeared but there are sequelae (the name or manifestation of the sequelae should be indicated when recording);
- Remission: AE improves symptoms with treatment.

5. **Serious adverse events**

Serious adverse events are those that occur during clinical trials that cause death or serious deterioration of health status, including fatal illness or injury, permanent defects in body structure or function, the need for hospitalization or prolonged hospitalization, or the need for medical or surgical intervention to avoid permanent defects in body structure or body functions; Events that lead to fetal distress, fetal death, or congenital anomalies or birth defects.

6. Reporting procedures, contact information

- In order to ensure the safety of subjects, any serious adverse event that occurs between the subject's signing of the informed consent form and the end of the study, whether or not related to the investigational medical device, must be reported to the company within 24 hours of becoming aware of its occurrence;
- For serious adverse events, investigators follow up and within 24 hours of obtaining follow-up information, the recurrence, complication or progression of the original serious adverse event must be reported as a follow-up event to the original event. Serious adverse

events considered to be completely unrelated to previously reported serious adverse events should be reported separately as a new serious adverse event;

- Investigators should collect all information of subjects with serious adverse events, fill in the serious adverse event report form, determine the correlation between SAE and the study device, sign, and fax the SAE report to the company within 24 hours. After receiving the SAE report, the company will report to the Ethics Committee of the Center, the State Medical Products Administration, the Medical Device Supervision Department of the Hebei Provincial Drug Administration, and the Health and Family Planning Commission of Hebei Province by telephone or fax within the working days of the same day.

In addition to the above situation, serious adverse events that occur during the test of the subject, regardless of whether it is related to the research device, the investigator should immediately take appropriate treatment measures for the subject to ensure the safety of the subject.

The original serious adverse event report form and fax acknowledgement must be kept at the study site along with the original record form.

7. Equipment defects

- If the investigator or physician finds that the device has design defects before use, the trial should be stopped immediately and notify the clinical trial office and the ethics committee of the clinical institution within 24 hours, and notify the sponsor within 48 hours, and the sponsor and the investigator should re-conduct the risk assessment of the product according to the defect content, and if necessary, re-conduct the pre-clinical trial research analysis in accordance with the Administrative Measures for the Registration of Medical Devices (Order No. 4 of the State Food and Drug Administration). Clinical trials can not be resumed until the defects have been re-evaluated to eliminate them, and ethical approval should be re-conducted before the trial;
- If the device is found to be defective and causes adverse events after use, it should be handled in accordance with the requirements in 1 above;
- If the sponsor finds defects in the device during the trial, it shall notify the test institution, ethics institution and researcher within two hours after the discovery, and at the same time terminate the clinical trial of the device, and declare it in writing to the Food and Drug

Administration on record within 48 hours; If there are no adverse events during the observation period, the patient should continue to follow up and observe in accordance with the requirements of the plan, and if necessary, the follow-up observation period should be extended until it is confirmed that the defective device will not cause adverse events to the patient, and all medical expenses for extending the follow-up period shall be borne by the organizer, and if adverse events occur, they should be handled in accordance with the requirements of "(3) reporting procedures and contact information";

- If the investigator finds that the device is defective during the trial, he should immediately stop the trial and notify the office of the clinical trial institution and the clinical trial within 2 hours The institutional ethics committee also notifies other research units and notifies the sponsor within 24 hours, the sponsor shall declare in writing to the registered drug administration within 48 hours, if there are no adverse events during the observation period, the patient should continue to follow up and observe in accordance with the requirements of the program, and if necessary, the follow-up observation period should be extended until it is confirmed that the defective device will not cause adverse events to the patient, and all medical expenses for extending the follow-up period shall be borne by the organizer, and if adverse events occur, they should be in accordance with "Reporting procedures, contact information" requirements.

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Annex

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营业执照

(副本)

类　　型　有限责任公司(自然人投资或控股)

注册资本　人民币100.0000万元整

成立日期　2015年09月07日

营业期限　2015年09月07日 至 2035年09月06日

住　　所　上海市普陀区真北路958号20幢437室

登记机关

2019 年 10 月 18 日