Informed Consent Form (ICF)

Name of investigational medical device:	Intracranial drug-eluting stents
Specification/Model of investigational device:	HC*IDES-2013N-00, HC*IDES-2017N-00, HC*IDES-2020N-00, HC*IDES-3020N-00, HC*IDES-3025N-00, HC*IDES-3025M-00, HC*IDES-3030N-00, HC*IDES-3030M-00, HC*IDES-4020N-00, HC*IDES-4025N-00, HC*IDES-4025M-00, HC*IDES-4030N-00, HC*IDES-4030M-00, HC*IDES-4040N-00, HC*IDES-4040M-00, HC*IDES-5025N-00, HC*IDES-5025M-00, HC*IDES-5030N-00, HC*IDES-5030M-00, HC*IDES-5040N-00, HC*IDES-5040M-00, HC*IDES-2013N-12, HC*IDES-2017N-12, HC*IDES-2020N-12, HC*IDES-3020N-12, HC*IDES-3025N-12, HC*IDES-3025M-12, HC*IDES-3030N-12, HC*IDES-3030M-12, HC*IDES-4020N-12, HC*IDES-4025N-12, HC*IDES-4025M-12, HC*IDES-4030N-12, HC*IDES-4030M-12, HC*IDES-4040N-12, HC*IDES-4040M-12, HC*IDES-5025N-12, HC*IDES-5025M-12, HC*IDES-5030N-12, HC*IDES-5030M-12, HC*IDES-5040N-12, HC*IDES-5040M-12
Sponsor:	Shanghai HeartCare Medical Technology Co., Ltd
Agent:	Shanghai HeartCare Medical Technology Co., Ltd
Name of clinical trial protocol:	Evaluation of safety and efficacy of intracranial drug-eluting stents for symptomatic intracranial atherosclerotic stenosis: a prospective, multicenter, randomized controlled, superiority clinical trial
Clinical trial protocol No.:	SHXW-202301
ICF version No.:	V1.0
ICF version date:	2023-08-21

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Clinical trial institution: Henan Provincial People's Hospital

Principal investigator: Li Tianxiao

Distinguished sir/madam,

You are invited to participate in a clinical trial involving medical devices. The following describes the background, objectives, methods, potential benefits, risks or inconveniences, and your rights related to this trial. Please read this informed consent carefully before deciding to participate.

This informed consent provides information to help you decide whether to join this clinical trial. The lead institution for this trial is Henan Provincial People's Hospital, where the research is conducted under the supervision of Director Li Tianxiao from the Department of Cerebrovascular Diseases. If you have any questions, please ask the research physician responsible for this trial to ensure you fully understand the details. Your participation in this trial is based on voluntary principle. Please sign the statement in the informed consent form after reading the following data, if you participate in the clinical study of your own accord.

1. Study name, Objectives, and Background

1.1. Study name

Evaluation of safety and efficacy of intracranial drug-eluting stents for symptomatic intracranial atherosclerotic stenosis: a prospective, multicenter, randomized controlled, superiority clinical trial.

1.2. Objectives

To validate the safety and efficacy of intracranial drug-eluting stents manufactured by Shanghai HeartCare Medical Technology Co., Ltd in the treatment of symptomatic intracranial atherosclerotic stenosis.

1.3. Background

Intracranial atherosclerotic stenosis (ICAS) is a significant cause of ischemic stroke occurrence and recurrence worldwide. In North America, ICAS accounts for 8% to 10% of stroke etiologies, while in Asia, it constitutes 30% to 50%. In China, ICAS prevalence among stroke/transient ischemic attack (TIA) patients is as high as 46.6%.

Treatment options for intracranial atherosclerotic stenosis (ICAS) encompass medical therapy, surgical interventions, and endovascular procedures. Globally, surgical treatments, due to their higher complication rates, have not received widespread endorsement in guidelines. In contrast, medical and endovascular therapies continue to be investigated to establish the optimal approach for managing ICAS. Current evidence strongly supports medical therapy as the first-line treatment for ICAS. Notably, results from two pivotal randomized controlled trials (RCTs)—the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial in 2011 and the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) trial in 2015—have consistently shown that aggressive medical therapy is both more effective and safer than endovascular interventions. Furthermore, a comprehensive review in 2018 comparing stent placement with aggressive medical therapy for symptomatic ICAS (sICAS) reaffirmed that medical therapy remains the preferred initial treatment option over endovascular procedures for managing sICAS.

The evolution of endovascular treatments for intracranial atherosclerotic stenosis (ICAS) reflects ongoing efforts to explore safer and more effective approaches, despite varying outcomes from pivotal studies such as SAMMPRIS, VISSIT, and the Chinese Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS) trial, which did not establish the superiority of endovascular interventions over medical therapy alone. In real-world settings, due to persistent high risks of stroke recurrence under medical therapy, research continues to advance endovascular treatment methods, including material developments. Following SAMMPRIS, studies like the Wingspan Stent System Post-Market Surveillance (WEAVE) and multicenter registry data from China emphasize rigorous patient selection and refined procedural standards, highlighting improved safety and promising efficacy in treating sICAS at established neurointerventional centers. Insights from CASSISS underscore the ongoing focus on disease diagnosis, technological innovations, and advancements in interventional devices for future sICAS research.

Drug-eluting stents (DES) typically consist of a base layer and a drug-eluting

layer. The drug-eluting layer contains anti-proliferative drugs that are slowly released, inhibiting the proliferation and migration of vascular smooth muscle cells to prevent in-stent restenosis (ISR). Commonly used drugs in drug-eluting stents include paclitaxel and rapamycin. Theoretical considerations suggest that rapamycin-based drug-eluting stents may offer superior efficacy compared to paclitaxel-based ones. Paclitaxel, known for its cytotoxic properties, operates within a narrow therapeutic window, which poses a heightened risk of cytotoxic side effects due to its proximity to inhibitory and cytotoxic concentrations. In contrast, rapamycin, categorized as a cell inhibitor, features a broader therapeutic window between inhibitory and cytotoxic concentrations, thereby potentially enhancing safety relative to paclitaxel. Previous studies indicate that the use of drug-eluting stents or drug-coated balloons in endovascular interventions effectively mitigates ISR risk by suppressing neointimal proliferation. In China, institutions such as Xuanwu Hospital and Shanghai Changhai Hospital have achieved success rates exceeding 90% in treating intracranial atherosclerotic disease (ICAD) with drug-eluting stents. The primary intraoperative complication reported is branch occlusion, managed postoperatively with standard antiplatelet therapy. Notably, only one case reported ISR and symptomatic recurrence, with no instances of neurotoxic reactions; however, two cases experienced arterial aneurysm-like dilation. These findings underscore the technical feasibility of employing drug-eluting stents for patients with symptomatic ICAD resistant to rigorous medical treatment, leading to reduced ISR rates from 30% initially to 0-7% over the short term (6 months to 1 year). Importantly, most patients experiencing restenosis did not encounter stroke recurrence or drug-related neurotoxicity, underscoring the safety and efficacy of drug-eluting stents for ICAS treatment. Research focusing on coronary and carotid arteries suggests that drug-eluting stents may offer superior clinical and imaging outcomes compared to bare-metal stents for managing narrowings or ISR.

Based on the aforementioned points, drug-eluting stents have been validated for their safety and effectiveness in treating ICAS. Shanghai HeartCare Medical Technology Co., Ltd has independently developed an intracranial drug-eluting stent,

which has successfully undergone type testing at the National Medical Device Quality Supervision and Inspection Center in Tianjin, accredited by the State Administration of Drug Administration. It has received a favorable inspection report, confirming that the product design is finalized and meets the intended design specifications. Furthermore, the stent has undergone preclinical studies including animal experiments and risk-benefit analyses at Western Point Biotech (Chengdu) Co., Ltd., preliminarily demonstrating the safety and efficacy of this intracranial drug-eluting stent. With these achievements, the product is poised for clinical trials. There are plans in progress to initiate a prospective, multicenter, randomized controlled trial to assess the safety and effectiveness of the intracranial drug-eluting stent in treating symptomatic intracranial atherosclerotic stenosis.

2. Methods and Study Design

This study is a prospective, multicenter, randomized controlled superiority clinical trial to be conducted at multiple sites in China. The study aims to recruit 208 patients with symptomatic intracranial atherosclerotic stenosis (ICAS), with our center expecting to enroll 30 participants.

Participants or their guardians will sign an informed consent form (ICF) approved by the Ethics Committee. Eligible participants who meet the inclusion criteria and do not meet any exclusion criteria will be randomized using a central registration system. The intervention group will receive the intracranial drug-eluting stent manufactured by Shanghai HeartCare Medical Technology Co., Ltd., while the control group will be treated with the Wingspan Stent System produced by Stryker (Beijing) Medical Devices Co., Ltd. All participants will be followed up at the following intervals: during the surgery, within 7 days post-surgery or before discharge, at 30 days post-surgery, at 6 months, at 12 months, and at 24 months post-surgery.

The primary outcome measure is the incidence of in-stent restenosis (ISR) at 6 months post-surgery, which will be used to evaluate the safety and efficacy of the intracranial drug-eluting stent.

The study evaluated seven secondary outcomes: (1) success rate of device operation, which demonstrated successful stent implantation and coverage of the target lesion site, along with the successful withdrawal of the delivery system; (2) operation success rate, including successful stent implantation, absence of major adverse events during the procedure (such as death or stroke), and immediate postoperative residual stenosis < 50%; (3) in-stent restenosis rate at 12 months post-operation; (4) incidence of symptomatic stent restenosis at 6 months and 12 months post-operation; (5) Modified Rankin score (mRS) at 30 days, 6 months, and 12 months post-surgery; (6) National Institutes of Health Stroke Scale score (NIHSS) preoperatively and 6 months post-hospital discharge; (7) target lesion revascularization rates at 30 days, 6 months, and 12 months post-operation, defined as the need for any surgical or percutaneous intervention to restore blood supply to the target vessel. This study examines four safety indicators related to surgical outcomes: (1) stroke incidence at 30 days, 6 months, and 12 months post-surgery; (2) all-cause death rates at 30 days, 6 months, 12 months, and 24 months post-surgery; (3) incidence rates of device-related adverse events/serious adverse events at 30 days, 6 months, 12 months, and 24 months post-surgery; and (4) incidence rates of device defects. These measures will be used to verify the safety and efficacy of the intracranial drug-eluting stent manufactured by Shanghai HeartCare Medical Technology Co., Ltd., in treating symptomatic intracranial atherosclerotic stenosis. This study does not involve a central laboratory. All sample collection, utilization, and processing will be managed by our center.

3. Study Duration and Procedure

Your expected participation in this trial will last approximately 2 years, encompassing preoperative screening, surgery, and follow-up visits at 7 days post-surgery or before discharge, and at 30 days, 6 months, 12 months, and 24 months post-surgery.

4. Funding and Potential Conflicts of Interest

This trial is sponsored and funded by Shanghai HeartCare Medical Technology Co, Ltd. The researchers involved in this clinical trial do not own any equity (including shares) in Shanghai HeartCare Medical Technology Co., Ltd. or in companies that compete with its products. There are no conflicts of interest between Shanghai HeartCare Medical Technology Co., Ltd. and the researchers.

5. Potential Benefits

(1) Your intracranial atherosclerotic stenosis (ICAS) may be treated, potentially alleviating symptoms, improving your quality of life, and reducing the risk of disease recurrence.(2) Based on the randomization results, you will receive either the intracranial drug-eluting stent in the experimental group or the Wingspan Stent System (manufactured by Stryker (Beijing) Medical Devices Co., Ltd.) in the control group. Both stents will be provided free of charge by the sponsor.(3) You will receive professional medical care from doctors, along with close follow-up to guide your recovery.(4) By participating in this study, the medical data you provide may help other patients with similar conditions benefit in the future.

6. Potential Risks and Discomforts

Participation in this clinical trial and undergoing stent treatment carries potential risks similar to those associated with conventional stent implantation, including but not limited to:

Cerebrovascular perforator occlusion	Hypersensitivity and allergic reactions	Arrhythmias	Aneurysm
In-stent restenosis	Hyperperfusion syndrome	Poor stent apposition	Hypotension/Hypertension
Death	Failure to deliver the stent to the lesion site	Arterial dissection	Hemorrhage
Stroke	Infection and pain at the puncture site	Distal embolization	In-stent thrombosis
Fever	Pseudoaneurysm from femoral artery puncture	Adverse reactions to drugs, antiplatelet drugs, anticoagulants, or contrast agents	Thrombosis (acute, subacute, or late)
Thrombosis (acute, subacute, or late)	Hypercholesterolemia	Abnormal liver function tests	Arthralgia
Anemia	Diarrhea	Infection	Renal failure

Leukopenia	Thrombocytopenia	Hypercholesterolemia	Hypokalemia
Vascular occlusion	Vasospasm	Vascular perforation or rupture	/

Other unforeseen risks may also occur. If such situations arise, please promptly inform your research physician. They will provide proactive and comprehensive treatment to ensure your safety and rights.

Reproductive risks: Female participants who are breastfeeding or pregnant cannot participate in this trial. During the study period, if you become pregnant or suspect you are pregnant, it is crucial to inform the research physician immediately. If you plan to conceive within the next year, you should not participate in this trial. Participation may pose potential risks to sperm or eggs, potentially harming the child conceived during the study period. This harm has not been clinically confirmed and is unpredictable.

7. Treatment and Compensation for Trial-Related Injuries

If your health is compromised due to participation in this trial, please inform the research physician, who will take the necessary medical measures. According to Article 48 of the "Medical Device Clinical Trial Quality Management Regulations" of China, in the event of trial-related injuries, you are entitled to receive active treatment, and Shanghai HeartCare Medical Technology Co., Ltd will cover the medical expenses and provide economic compensation as stipulated by relevant laws.

Shanghai HeartCare Medical Technology Co., Ltd. has purchased insurance for this clinical trial. If you experience damage related to the trial, as judged by the researcher, they will provide active medical treatment. The insurance will offer appropriate compensation and indemnity. Any costs beyond the insurance coverage will be borne by the sponsor.

8. The treatment groups

Participants may be allocated to either the experimental group, receiving surgical treatment with the intracranial drug-eluting stent developed by Shanghai HeartCare

Medical Technology Co., Ltd. or the control group, receiving surgical treatment with the Wingspan Stent System from Stryker (Beijing) Medical Technology Co., Ltd.

9. Alternative Treatment Methods Outside of This Trial

If you choose not to participate in this clinical trial, you will not have access to the investigational medical devices used in this study. However, you still have the option to undergo surgical treatment using medical devices approved by the National Medical Products Administration (NMPA) for commercial use. Please note that you will be responsible for the costs associated with these devices.

Stent implantation is a recent emerging technology over the past 2-3 years. Apart from surgical treatment, pharmacotherapy is also a common clinical approach. You may opt for pharmacological treatment based on your condition, but specific treatment options should be discussed with your attending physician.

10. Confidentiality of Medical Records

The principal investigator is responsible for safeguarding your health, dignity, autonomy, and privacy, ensuring confidentiality of your personal information.

Your participation in the trial and your personal data collected during the trial are strictly confidential. The Ethics Committee, National Medical Products Administration, or the sponsor may access participant information as required by regulations, with a duty to maintain confidentiality. When the trial results are published, your personal identity or privacy will not be disclosed.

11. Free Medical Services and Other Related Benefits During the Trial

(1) After participating in this study, you will receive either the intracranial drug-eluting stent as determined by randomization or the control group treatment with the Wingspan Stent System (produced by Stryker (Beijing) Medical Device Co., Ltd.) provided free of charge by the sponsor.(2) During your participation in the study, various laboratory tests and examinations will be conducted, including routine tests such as complete blood count, blood biochemistry, coagulation function, as well as

head CTA, MRA, or DSA scans. These tests are part of standard care during surgical treatment, and even if you were not participating in the trial, they would generally be required for evaluation. The costs of these tests related to participation in the study will be covered by the sponsor (Results of the aforementioned tests conducted within the allowed preoperative period will not be repeated and will not be reimbursed if conducted before study participation). However, costs associated with treatments and tests required for other concurrent diseases are not covered.(3) If you are successfully enrolled in the study, follow-up imaging studies at 6 and 12 months post-surgery, including DSA or CTA scans, will be provided free of charge by the sponsor. Additionally, a subsidy of 1000 RMB for transportation and meals will be provided by the sponsor during each follow-up visit. This subsidy will be distributed uniformly upon completion of the 12-month follow-up based on the actual number of follow-up visits.

12. Voluntary Participation and Withdrawal from the Trial

You have the option to decline participation in this trial or withdraw at any time after informing the researcher without fear of discrimination or retaliation. Your medical treatment and rights will not be affected by your decision. If you require alternative diagnosis/treatment, fail to adhere to the trial protocol, or for any other valid reason, the researcher may terminate your continued participation in this trial.

You can learn about the progress related to the study at any time, and if you have any questions related to the study (e.g. rights and interests of the participant), or you have any discomfort or injury during the study, please contact (Investigator) _____at _____(Tel or mobile No.); and if you have any questions related to your rights and interests, contact the ethics committee of the Site at: _____.

Subject Informed Consent Statement

I have carefully read this informed consent form, and I have had the opportunity to ask questions, all of which have been answered to my satisfaction. I understand that participation in this trial is voluntary, and I may choose not to participate or withdraw at any time after informing the researcher, without fear of discrimination or retaliation. My medical treatment and rights will not be affected by this decision.

If I require alternative diagnosis/treatment, fail to adhere to the trial protocol, or for any other valid reason, the researcher may terminate my continued participation in this clinical trial.

I voluntarily consent to participate in this clinical trial, and I will receive a signed copy of the "Informed Consent Form."

Signature of the subject: _____ **Date:** _____

Tel: _____

Note: If the subject is unable to sign the informed consent form due to lack of capacity, their legal guardian or authorized representative should sign on their behalf.

Signature of guardian: _____ **Date:** _____

Relationship with subject: **Tel:** _____

Reason why the subject cannot sign: _____

Note: If the subject lacks reading ability, a notary or authorized witness will read the informed consent form and other pertinent information to them, witness the consent process, and sign the informed consent form on their behalf.

Signature of an impartial witness: **Date:** _____

Tel: _____

Statement of Investigator

I confirm that I have accurately informed the subject of the contents of the Informed Consent Form and answered the questions raised by the subject, and the subject is willing to participate in this clinical trial.

Signature of the Investigator: **Date:** _____

Tel: _____