

CLINICAL STUDY PROTOCOL

Project Title: Traditional approach versus Flow Diverter for unruptured intracranial wide-neck bifurcation aneurysms: a prospective international multicenter randomized controlled study (FD-BWA study)

Protocol Version/Date: V1.1 / 2025.12.16

Lead Unit: Nanfang Hospital, Southern Medical University

Address of Lead Unit: No. 1838, Guangzhou Avenue North, Baiyun District, Guangzhou City, Guangdong Province

Research Department / Principal Investigator: Neurosurgery Department / Feng Wenfeng

Sponsor/Address: Nanfang Hospital, Southern Medical University / No. 1838, Guangzhou Avenue North, Baiyun District, Guangzhou City, Guangdong Province

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STUDY SYNOPSIS

Protocol Title	Traditional approach versus Flow Diverter for unruptured intracranial wide-neck bifurcation aneurysms: a prospective international multicenter randomized controlled study (FD-BWA study)
Sponsor	Nanfang Hospital, Southern Medical University
Principal Investigator	Feng Wenfeng
Lead Unit	Nanfang Hospital, Southern Medical University
Study Population	Patients with unruptured intracranial wide-neck saccular bifurcation aneurysms.
Study Objective	Primary objective: To verify whether the complication rate at 1 year post-surgery in unruptured intracranial wide-neck bifurcation aneurysms treated with the traditional approach (stent-assisted coiling) is lower than that with flow diverter (Pipeline™ (Flex/Shield)) treatment. Secondary objective: To investigate the imaging cure rate (Cekirge-Saatci grade 1 / Raymond-Roy grade I) and stability rate (Cekirge-Saatci grade 5, Raymond-Roy not applicable) at 1, 2, and 5 years post-surgery in both groups.
Study Groups	Experimental group (flow diverter), Control group (traditional stent-assisted coiling)
Study Design	This is a prospective, international, multicenter, randomized controlled clinical trial, with open-label treatment and blinded endpoint assessment.
Study Duration	5 years
Sample Size	266
Non-study Drugs	1. Both groups receive the same antiplatelet regimen: oral aspirin (aluminum-magnesium aspirin, indobufen) and ticagrelor (prasugrel, clopidogrel: platelet function test and genotyping required to meet the standard) 3-5 days preoperatively, dual antiplatelet for 6 months postoperatively. 2. Long-term aspirin (aluminum-magnesium aspirin, indobufen) after 6 months. 3. Platelet function test and genotyping are recommended preoperatively, and antiplatelet therapy adjusted accordingly.
Inclusion Criteria	1. Age 18-75 years; 2. Diagnosis of unruptured intracranial, bifurcation, saccular, wide-neck aneurysm by DSA/CTA/MRA; 3. Patients who can understand the purpose of the trial, voluntarily participate and sign the informed consent form.
Exclusion Criteria	1. Patients with two or more multiple aneurysms that all require treatment within 1 year;

	2. Concomitant cerebrovascular diseases such as arteriovenous malformation, moyamoya disease; 3. Ruptured aneurysms and narrow-neck aneurysms; 4. Patients who have had a stroke (cerebral hemorrhage, cerebral infarction) within the past 1 month; 5. Extremely poor clinical condition, modified Rankin Score ≥ 3; 6. Patients already scheduled for surgery/interventional procedure within 3 months; 7. Patients deemed unsuitable for interventional treatment by the investigator (e.g., no suitable vascular access, excessively tortuous vessels, difficulty delivering stent); 8. Patients unsuitable for anesthesia or endovascular surgery, such as major diseases of heart, lung, liver, spleen, kidney, brain tumors, severe active infections, disseminated intravascular coagulation, severe mental illness; 9. Patients unable to receive antiplatelet or anticoagulant therapy; 10. Patients who have had or may have severe reactions to contrast media precluding pre-treatment medication; 11. Patients with a definite history of allergy to cobalt-chromium, nickel-titanium alloy materials; 12. Participation in other drug or medical device clinical trials before enrollment without reaching the primary endpoint timeframe; 13. Pregnant or breastfeeding women; 14. Patient's life expectancy less than 12 months; 15. Investigator judges that the patient has poor compliance and cannot complete the study as required.
Efficacy Endpoint Analysis	Primary endpoint: any stroke, all-cause death events within 1 year post-surgery. Secondary endpoints: imaging cure rate (Cekirge-Saatci grade 1 / Raymond-Roy grade I) and stability rate (Cekirge-Saatci grade 5, Raymond-Roy not applicable) at 1, 2, and 5 years post-surgery. Other observational indicators: 1. Incidence of transient ischemic attack (TIA) at 6 months, 1, 2, and 5 years post-surgery; 2. Rate of severe disability (mRS>2) at 6 months, 1, 2, and 5 years post-surgery; 3. Rate of significant in-stent stenosis ($>50\%$) at 6 months, 1, 2, and 5 years post-surgery; 4. Immediate technical success rate; 5. Target vessel retreatment rate at 6 months, 1, 2, and 5 years post-surgery; 6. Asymptomatic branch coverage stenosis and occlusion rate at 6 months, 1, 2, and 5 years post-surgery; 7. Any stroke, all-cause death events at 2 and 5 years post-surgery. Definitions: 1. Stroke defined as: acute focal or global neurological dysfunction

	due to vascular injury of brain, spinal cord or retina caused by hemorrhage or infarction, symptom duration ≥ 24 hours, including symptomatic branch stenosis/occlusion due to branch coverage; 2. TIA: transient focal neurological dysfunction due to brain, spinal cord or retinal ischemia, symptom duration < 24 hours, without acute infarction; 3. Technical success: Experimental group: successful FD implantation in parent artery covering aneurysm neck; Control group: a) successful coil implantation into aneurysm sac; b) auxiliary stent implanted in parent artery covering aneurysm neck; 4. Retreatment rate: target lesion retreatment rate, including target aneurysm and target parent artery retreatment rate; 5. Raymond-Roy grade: Class I: complete occlusion, no contrast filling in sac or neck; Class II: neck remnant, sac obliterated, contrast in neck; Class III: aneurysm remnant, contrast in sac. 6. Cekirge-Saatci grade: Grade 1: complete aneurysm occlusion. If branch incorporated into sac (originating from any part of aneurysm), subanalysis: IA complete occlusion + branch patent; IB complete occlusion + branch caliber reduction; IC complete occlusion + no antegrade branch filling. Grade 2: neck filling. Grade 3: incomplete occlusion with aneurysm filling. Grade 4: aneurysm filling – specifically for immediate post-procedure DSA after extrasaccular/intrasaccular flow modification: 4A with contrast stagnation, 4B without. Grade 5: stable remodeling after flow modification: neck filling unchanged or decreased; requires at least two consecutive control angiograms at least 6 months apart, total ≥ 1 year; exceptions for cases with branch filling from sac with different appearance (e.g., tortuous/dilated) as long as connected to parent artery without sac filling, a single control may suffice.
Safety Analysis	Primary safety: perioperative complication rate. Secondary safety: follow-up complication rate.
Statistical Analysis	Baseline and efficacy analyses based on Full Analysis Set (FAS); safety based on Safety Analysis Set (SAS). All tests two-sided, $P < 0.05$ considered significant. Baseline descriptive summary; chi-square for categorical, t-test or nonparametric for continuous. Primary endpoint: FAS, chi-square, Cox PH model for HR and 95% CI for composite events (any stroke, all-cause death) within 1 year. Secondary: general principles; binary: chi-square, generalized linear model for RR and 95% CI; survival: Cox PH. Safety endpoints: Cox PH or Poisson/negative binomial for rare events.
Follow-up	Collection of cranial MRA/CTA/DSA imaging and clinical assessments at baseline, 6 months, 1, 2, and 5 years post-intervention.
Statistical Methods	t-test, chi-square, etc.
Anticipated Timeline	2025.06.01 – 2030.06.31

LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
FD	Flow Diverter
IA	Intracranial Aneurysm
DSA	Digital Subtraction Angiography
FAS	Full Analysis Set
SAS	Safety Analysis Set

STUDY FLOW CHART

Item	Screening Period			Treatment Period (days) / Immediate Post-op	Assessment Period	Exit	
	- 3d	- 2d	- 1d				
				0	30d post-op	6m,1y,2y,5y post-op	
Informed Consent	☒	☐	☐				
Demographics	☒	☐	☐				
Inclusion/Exclusion Criteria	☒	☐	☐				
Medical History	☒	☐	☐				
Neurological Exam	☒	☐	☐	☒	☒	☒	
Medications	☒	☒	☒				☒
Blood Tests	☒	☐	☐				☒ (if needed)
Surgery (FD/Traditional)	☐	☐	☐	☒			
Post-op Complications	☐	☐	☒	☒	☒		
mRS Score	☐	☐	☒	☒	☒	☒	☒
DSA/Imaging (Raymond/Cekirge-Saatci)	☐	☐	☐	☒		☒	☒
Recurrence & Retreatment	☐	☐	☐			☒	☒
Adverse Events	☒	☒	☒	☒		☒	☒

1. STUDY BACKGROUND

1.1 Bifurcation Intracranial Aneurysms

The population prevalence of intracranial aneurysms is 3.2% [1]. Rupture leading to subarachnoid hemorrhage carries high morbidity, with a total mortality rate of 28%–67% [2, 3]. Vascular bifurcations are prone to forming intracranial aneurysms, accounting for 26.0%–64.7% of all intracranial aneurysms, and they are highly prone to rupture, representing approximately 60% of all ruptured intracranial aneurysms [4, 5]. Currently, treatment for bifurcation intracranial aneurysms mainly includes surgical clipping and endovascular therapy. Surgical clipping offers relatively definite effects but is associated with greater trauma and longer postoperative recovery [6]. Especially for distal bifurcation aneurysms, due to small vessel diameters, numerous branches, and narrow surgical working space, the asymmetry of the bifurcation significantly influences vessel diameter changes and hemodynamics, further increasing treatment complexity [7], such as posteroinferiorly projecting carotid-A1 junction aneurysms [8], where surgical manipulation is complex, aneurysms are often small and elongated, and the anatomical location limits the surgical field, increasing difficulty and complexity.

With the development and application of new endovascular devices in recent years, endovascular therapy has gradually become the mainstream treatment choice for bifurcation intracranial aneurysms [1]. Traditional endovascular treatment for bifurcation intracranial aneurysms primarily involves coil embolization, but often requires combination with multiple stents or balloons [9]. However, due to the increased foreign material within the parent artery from multiple devices, ischemic complications are more likely [10]. Furthermore, because bifurcation aneurysms tend to form at branches forming a smaller angle with the main artery, where hemodynamic stress is greater, endovascular catheterization becomes more challenging, increasing the difficulty of endovascular treatment [11].

1.2 Flow Diverter Pipeline and Intracranial Bifurcation Aneurysms

In recent years, endovascular therapy has advanced rapidly, especially with the advent of flow diverters, marking a new milestone in intracranial aneurysm treatment [12, 13]. Different from previous treatment concepts, flow diverters innovate by focusing on parent artery reconstruction, reducing inflow velocity and flow into the aneurysm, promoting intra-aneurysmal thrombosis and neointimal growth at the neck, thereby achieving aneurysm occlusion [12]. Multiple multicenter clinical studies on the Pipeline™ Embolization Device (PED, ev3/Medtronic, USA) have recently been conducted in North America and Europe. Becske et al. [14, 15] reported results from the North American multicenter prospective study (PUFS), showing complete occlusion rates of 73.6%, 86.8%, and 93.4% at 180 days, 1 year, and 3 years follow-up for complex internal carotid artery aneurysms treated with PED. O'Kelly et al. [16] showed a near-complete or better occlusion rate of 90% at 1 year follow-up for complex intracranial aneurysms treated with PED. Many domestic and international studies [15-18] have confirmed the efficacy of PED for complex intracranial aneurysms. Initially developed for large/giant aneurysms, fusiform aneurysms, etc.,

where conventional embolization was unsatisfactory, the initial indication was mainly large/giant internal carotid artery aneurysms proximal to the posterior communicating artery origin. Recently, flow diverters have been used to treat aneurysms in almost all intracranial locations, varying sizes, and pathologies, such as dissecting aneurysms, blood blister-like aneurysms, posterior circulation aneurysms, and bifurcation aneurysms.

Compared to traditional endovascular approaches, placing a flow diverter at a bifurcation may be technically easier [19], with extremely low recurrence rates. Moreover, with increasing use of flow diverters in bifurcation aneurysms, multiple studies suggest their efficacy is not inferior to traditional methods. For instance, Saatci et al. reported a 1-year occlusion rate of 95% for middle cerebral artery bifurcation aneurysms treated with flow diverters [20]. Thomas et al. [21] conducted a prospective cohort study reporting outcomes in 87 middle cerebral artery bifurcation aneurysms treated with flow diverters; 88.5% had imaging follow-up at a median of 16.3 months, with complete occlusion in 59% and near-complete occlusion (90-99%) in others. Mounayer et al. [22] reported a prospective cohort of 32 cases showing a 1-year occlusion rate of 97.3%; 29 patients (90.6%) had mRS 0-1, and 3 (9.4%) had mRS 2. In comparison, recurrence rates after conventional stent-assisted coiling for bifurcation aneurysms at 12 months, 18 months, and 3 years were 5.1%, 7.1%, and 11.9% respectively [23]. Although bifurcation aneurysms treated with flow diverters may occlude slowly or remain unoccluded on long-term imaging, recurrence is rare [21], thus achieving long-term stability and potentially "clinical cure" rather than merely imaging cure. Therefore, Saatci et al. [24] proposed a novel grading system based on Raymond-Roy, introducing a grade for stable vascular remodeling with flow modification, i.e., neck filling that remains unchanged or decreases over at least two angiograms spaced ≥ 6 months, considered stable aneurysm. Consequently, due to the very low recurrence rate with flow diverters, more scholars are applying them to bifurcation aneurysms.

However, due to the basic design of flow diverters, coverage of bifurcation vessels might lead to hypoperfusion in dependent vascular territories and symptomatic ischemia, causing significant controversy regarding their use at bifurcation sites [14, 25]. A previous meta-analysis found a total complication rate as high as 22% for flow diverter treatment of bifurcation aneurysms [26], higher than the complication rate (7%-8%) for other conventional methods like stent-assist [27, 28]. Nevertheless, with increasing application, the safety profile is being reassessed. Saatci et al. [20] reported an 8.6% complication rate in middle cerebral artery bifurcations. Thomas et al. [21] showed ischemic and hemorrhagic complication rates of 8% and 1.1%, respectively, with symptomatic and permanent complication rates of 5.7% and 2.3% after flow diverter treatment for bifurcation aneurysms. In contrast, a meta-analysis of stent-assisted coiling for intracranial bifurcation aneurysms reported a postoperative complication rate of 8.9% [27]. Therefore, the safety of flow diverters for bifurcation aneurysms still requires further investigation.

In summary, there is considerable controversy regarding flow diverter treatment for wide-neck bifurcation aneurysms. Whether the postoperative complication rate of traditional stent-assisted coiling is lower than that of flow diverter treatment remains unclear. Previous studies are either retrospective or small prospective cohorts. A prospective randomized controlled study is urgently needed to evaluate the true effect

of its application, providing robust evidence for clinical practice and subsequent research, thereby better guiding clinical practice and meeting clinical needs.

2. STUDY OBJECTIVES

2.1 Primary Objective

This study's primary objective is to verify whether the complication rate at 1 year post-surgery in unruptured intracranial wide-neck bifurcation aneurysms treated with the traditional approach (stent-assisted coiling) is lower than that with flow diverter (Pipeline™ (Flex/Shield)) treatment.

2.2 Secondary Objective

To investigate the imaging cure rate (Cekirge-Saatci grade 1 / Raymond-Roy grade I) and stability rate (Cekirge-Saatci grade 5, Raymond-Roy not applicable) at 1, 2, and 5 years post-surgery in both groups.

3. STUDY ENDPOINTS

3.1 Primary Endpoint

Any stroke, all-cause death events within 1 year post-surgery.

3.2 Secondary Endpoints

Imaging cure rate (Cekirge-Saatci grade 1 / Raymond-Roy grade I) and stability rate (Cekirge-Saatci grade 5, Raymond-Roy not applicable) at 1, 2, and 5 years post-surgery.

4. STUDY DESIGN

4.1 Overall Design

This clinical study is a prospective, international, multicenter, randomized (1:1) controlled trial, with open-label treatment and blinded endpoint assessment. 266 patients will be enrolled. After signing informed consent, patients meeting inclusion/exclusion criteria will be randomized 1:1 via random number method into experimental group (flow diverter) and control group (traditional approach). Diagnosis and treatment standards for intracranial aneurysms refer to the Chinese Guidelines for the Diagnosis and Treatment of Unruptured Intracranial Aneurysms 2021 and the Chinese Guidelines for the Treatment of Intracranial Aneurysms with Flow Diverters 2023, confirming clinical indication for surgery. Subjects randomized to the experimental group will undergo flow diverter implantation (possibly combined with coiling); those in the control group will undergo stent-assisted coil embolization. Preoperative evaluation, intraoperative management, postoperative medication and management are consistent for all subjects. Safety assessments and survival follow-

up, including imaging efficacy evaluation, will be conducted at 6 months, 1, 2, and 5 years post-surgery.

4.2 Randomization and Blinding

4.2.1 Randomization

Patients meeting inclusion/exclusion criteria will be randomized in a 1:1 ratio to experimental or control group. Randomization method: central randomization, using computer-generated random numbers in a 1:1 ratio at the central site.

4.2.2 Blinding/Unblinding

This study will be conducted as a single-blind study with blinded endpoint assessment, i.e., personnel evaluating imaging data are blinded. To minimize potential bias from investigators and subjects across centers on the primary endpoint and to ensure more objective and valid results, a Clinical Endpoint Committee will be established. The committee will consist of at least 3 physicians with experience in imaging, neurology, or surgery/intervention, unrelated to this study, who will independently and blindly review clinical endpoint events.

5. STUDY POPULATION

The study population consists of 266 patients with intracranial aneurysms from 12 domestic and international centers.

5.1 Diagnostic Criteria

Diagnosis of intracranial aneurysm according to the Chinese Guidelines for the Diagnosis and Treatment of Unruptured Intracranial Aneurysms 2021 and the Chinese Guidelines for the Treatment of Intracranial Aneurysms with Flow Diverters 2023, etc.

5.2 Inclusion Criteria

1. Voluntarily sign informed consent form;
2. Age 18-75 years;
3. Diagnosis of unruptured, bifurcation, saccular, wide-neck intracranial aneurysm by CTA/MRA/DSA;
4. Able to understand the purpose of the trial.

5.3 Exclusion Criteria

1. Patients with two or more multiple aneurysms that all require treatment within 1 year;
2. Concomitant cerebrovascular diseases such as arteriovenous malformation, moyamoya disease;
3. Ruptured aneurysms and narrow-neck aneurysms;

4. Patients who have had a stroke (cerebral hemorrhage, cerebral infarction) within the past 1 month;
5. Extremely poor clinical condition, modified Rankin Score ≥ 3 ;
6. Patients already scheduled for surgery/interventional procedure within 3 months;
7. Patients deemed unsuitable for interventional treatment by the investigator (e.g., no suitable vascular access, excessively tortuous vessels, difficulty delivering stent);
8. Patients unsuitable for anesthesia or endovascular surgery, such as major diseases of heart, lung, liver, spleen, kidney, brain tumors, severe active infections, disseminated intravascular coagulation, severe mental illness;
9. Patients unable to receive antiplatelet or anticoagulant therapy;
10. Patients who have had or may have severe reactions to contrast media precluding pre-treatment medication;
11. Patients with a definite history of allergy to cobalt-chromium, nickel-titanium alloy materials;
12. Participation in other drug or medical device clinical trials before enrollment without reaching the primary endpoint timeframe;
13. Pregnant or breastfeeding women;
14. Patient's life expectancy less than 12 months;
15. Investigator judges that the patient has poor compliance and cannot complete the study as required.

5.4 Withdrawal Criteria

If a subject withdraws from the study for any reason, the reason must be recorded, including but not limited to:

1. Subject withdraws informed consent;
2. Sponsor terminates the study;
3. Serious adverse event affecting the subject's continued participation;
4. Serious protocol violation/deviation;
5. Pregnancy;
6. Poor compliance;
7. Lost to follow-up;
8. Investigator and/or sponsor believe that the subject's medical condition may endanger the subject's safety or continuing the study would harm the subject's health;
9. Death;
10. Other.

5.5 Termination Criteria

Criteria for terminating the trial (the trial will be terminated if any of the following are met):

1. Serious safety issues occur during the trial, i.e., the rate of severe cerebral hemorrhage or ischemia complications in either experimental or control group exceeds 30%;
2. A major error is found in the clinical trial protocol during the trial;

3. The Ethics Committee requests termination of the trial.

6.1 Investigational Treatment Technique or Device:

Pipeline™ (Flex/Shield) Flow Diverter (PED, ev3 / Medtronic, USA)

6.2 Non-study Drugs:

Supportive or rescue drugs used for prophylactic, diagnostic, or therapeutic purposes in this study, which are part of standard treatment for diagnosed diseases, are considered non-study drugs. Antiplatelet regimen: both groups receive the same antiplatelet regimen, i.e., oral aspirin (aluminum-magnesium aspirin, indobufen) and ticagrelor (prasugrel, clopidogrel: platelet function testing and genotyping are required to meet the standard) 3-5 days preoperatively, dual antiplatelet therapy for 6 months postoperatively, and long-term aspirin (aluminum-magnesium aspirin) thereafter. It is recommended that platelet function testing and genotyping be routinely performed preoperatively, and the antiplatelet regimen adjusted according to the results.

6.3 Surgical Procedures

6.3.1 Traditional Approach (Stent-Assisted Coiling):

The patient is placed in a supine position. After satisfactory general anesthesia, the right groin area is routinely disinfected and draped. The right femoral artery sheath is replaced with an 8F sheath. Systemic heparinization is administered, followed by continuous pressurized infusion. A 6F long sheath plus a 5F multifunction catheter are advanced with a Terumo guidewire, and the long sheath is positioned in the left vertebral artery. A micro-guidewire is used with a microcatheter to selectively catheterize the left posterior cerebral artery P2 segment, and then the microcatheter is advanced into the aneurysm. Through the microcatheter, one coil is semi-deployed to form a framing coil, then one stent is deployed through the stent catheter to cover the aneurysm neck. After the first framing coil is detached, several additional coils are sequentially deployed to embolize the aneurysm. Follow-up angiography shows no opacification of the aneurysm, parent artery patency, and no intracranial hemorrhage. The microcatheter and stent catheter are withdrawn. At the end of the procedure, the right femoral artery sheath is removed, the right femoral artery puncture site is closed with an 8F vascular closure device, and a compression device is applied for hemostasis.

6.3.2 Flow Diverter Approach:

The patient is placed in a supine position. The right groin area is routinely disinfected and draped. Local infiltration anesthesia is applied at the puncture site, and the right femoral artery is punctured using the Seldinger technique. An 8F sheath is inserted, systemic heparinization is administered, and continuous pressurized infusion is started. A 6F long sheath is advanced to the origin of the right internal carotid artery with the assistance of a Terumo guidewire and a multifunction catheter. A 5F intermediate catheter is advanced inside the long sheath to the petrous segment of the right internal carotid artery. 3D cerebral angiography is performed, and after a

suitable working angle is obtained, a stent catheter is advanced to the right middle cerebral artery M3 segment with micro-guidewire assistance. Manual injection shows no hemorrhage, confirming the true lumen. After calibration and measurement, one flow diverter stent is deployed to cover the aneurysm neck. Follow-up angiography shows good stent position, good wall apposition, parent artery stenosis unchanged from pre-operatively, and DynaCT shows no intracranial hemorrhage. The microcatheter and guide catheter are withdrawn, and the femoral artery puncture site is sutured with a closure device and a compression device is applied.

7. STUDY METHODS AND PROCEDURES

All subjects must sign informed consent before screening. Subjects who meet screening criteria may enter this study. Surgical treatment is performed according to the protocol for subjects in the experimental and control groups, respectively.

At the start of the study, patients will be assigned to receive flow diverter implantation or stent-assisted coil embolization based on computer-generated random numbers (randomization is like tossing a coin). There is a 50% probability of being assigned to the flow diverter group or the traditional approach group. Neither the patient nor the physician can know or choose the treatment in advance. Treatment observation will last for 3 days.

Treatment group: flow diverter treatment;
Control group: stent-assisted coil treatment.

Day 30 post-treatment: outpatient follow-up, medical history collection.
Six months post-treatment: inpatient cerebral angiography review, with follow-up during the stay.
One year post-treatment: inpatient cerebral angiography review, with follow-up during the stay.
Two years post-treatment: inpatient cerebral angiography review, with follow-up during the stay.
Five years post-treatment: inpatient cerebral angiography review, with follow-up during the stay.

7.1 Screening Period

All subjects must complete screening-related examinations before enrollment, and screening will be performed according to the inclusion/exclusion criteria.

1. Sign informed consent form.
2. Record demographic data: date of birth, sex, initials of name.
3. Medical history and physical examination: including vital signs, height, weight, systemic physical examination; hypertension, diabetes, hyperlipidemia, coronary heart disease, etc.
4. Other laboratory tests: complete blood count (red blood cell count, white blood cell count, hemoglobin, platelet count, etc.); liver function (albumin, globulin, total protein); lipids (triglycerides, high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein).

5. Imaging examinations: MRA, CTA, or cerebral DSA, etc.
6. Morphological characteristics of intracranial aneurysm: location, morphology, size, number, and previous treatment history, etc.

7.2 Treatment Period

7.2.1 Randomization Assessment Form

Patients will be assessed for eligibility by the responsible physician according to the previously described checklist. This form will be stored together with the study patient's documents at the participating institution.

7.2.2 Randomization

This clinical study considers controlling for balance across participating centers. The randomization system assigns randomization numbers and treatment groups. At the time of randomization, the investigator or clinical research coordinator (CRC) assists the investigator to log into the EDC system, confirms the basic information and impact factors of the subject to be randomized, and triggers randomization through interaction between the EDC and the randomization system, obtaining the corresponding randomization number and treatment group. The randomization number corresponds to a unique subject and cannot be reused once assigned.

This clinical trial recommends randomization after intraoperative DSA, but also accepts randomization based on pre-operative DSA/CTA/MRA imaging confirming that inclusion/exclusion criteria are met.

7.2.3 During the surgical procedure, the following data will be recorded

1. Surgery duration.
2. Anesthesia method: local anesthesia, general anesthesia.
3. Surgical method: stent-assisted coiling, flow diverter implantation.
4. FD implantation: diameter, length, type, number.
5. Coils: model, type, number.
6. Stents: diameter, length, type, number.
7. Medication history.
8. Adverse events / serious adverse events.

7.3 Follow-up Period

Follow-up time points follow routine clinical practice. Routine cranial CT is performed for post-operative patients; patients with obvious ischemic symptoms undergo further cranial MRI. Cerebral DSA is performed at 6 months, 1 year, 2 years, and 5 years post-surgery. After enrollment, clinical follow-up will be conducted, and we will collect the aforementioned blood routine, liver function, lipids, as well as patient height, weight, and systemic physical examination. Clinical follow-up will be completed via hospitalization, outpatient visits, and telephone calls. All patients will complete at least 1 year of follow-up.

8. EVALUATION INDICES

8.1 Safety Evaluation

Adverse complications during the perioperative period and follow-up period: incidence of stroke, transient ischemic attack, and death, etc.

8.2 Efficacy Evaluation

To investigate the imaging cure rate (Cekirge-Saatci grade 1 / Raymond-Roy grade I) and stability rate (Cekirge-Saatci grade 5, Raymond-Roy not applicable) at 1, 2, and 5 years post-surgery in both groups. This study uses centralized assessment across multiple centers. Clinical data of all enrolled patients will be aggregated, re-numbered, and then jointly evaluated by three neurointerventional physicians with deputy senior professional titles or above and one radiologist with a senior professional title from multiple centers.

Note: Stroke is defined as: acute focal or global neurological dysfunction due to vascular injury of brain, spinal cord or retina caused by hemorrhage or infarction, symptom duration ≥ 24 hours.

Transient ischemic attack is defined as: transient focal neurological dysfunction due to brain, spinal cord or retinal ischemia, symptom duration < 24 hours, without acute infarction.

9.1 Definition of Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient or subject who is administered study treatment, and it does not necessarily have a causal relationship with the treatment. Therefore, an AE can be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study device. AEs include serious adverse events (SAEs) and non-serious adverse events.

9.2 Definition of SAE

SAE refers to any medical event that occurs during a clinical trial and results in hospitalization or prolongation of hospitalization, disability, impairment of working ability, life-threatening condition, death, or congenital anomaly. It includes the following medical events:

1. Events that result in death;
2. Life-threatening events (defined as immediate risk of death at the time of the event);
3. Events that require hospitalization or prolongation of hospitalization;
4. Events that result in permanent or severe disability/functional impairment/impairment of working ability;
5. Congenital anomaly or birth defect;
6. Other important medical events (defined as events that jeopardize the subject or require intervention to prevent any of the above outcomes).

9.3 Recording, Collection, Reporting, and Handling of Adverse Events

9.3.1 Definition of Adverse Event (AE):

An AE is any adverse medical event occurring in a clinical study subject that is temporally related to the use of the study intervention, whether or not considered related to the study intervention. Therefore, an AE can be any adverse and unintended sign (including abnormal laboratory findings), symptom, or disease (new or worsening) that is temporally associated with the use of the study intervention.

Definition of Serious Adverse Event (SAE):

SAE refers to any medical event that occurs during a clinical trial and results in hospitalization or prolongation of hospitalization, disability, impairment of working ability, life-threatening condition, death, or congenital anomaly. It includes the following medical events:

- 1) Events that result in death;
- 2) Life-threatening events (defined as immediate risk of death at the time of the event);
- 3) Events that require hospitalization or prolongation of hospitalization;
- 4) Events that result in permanent or severe disability/functional impairment/impairment of working ability;
- 5) Congenital anomaly or birth defect;
- 6) Other important medical events (defined as events that jeopardize the subject or require intervention to prevent any of the above outcomes).

Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR):

A suspected unexpected serious adverse reaction is a serious adverse reaction whose nature and severity are not consistent with the available information in the approved package insert or product characteristics summary of the study device.

9.3.2 Collection, Reporting, and Handling of AEs

All AEs related to the procedures specified in the protocol that occur after signing the informed consent form and before use of the study device must be recorded in the source documents and/or case report forms.

AE records should include: description of the AE and all related symptoms, onset time, severity, duration, relationship to the study device, actions taken, and final outcome and resolution. AE records must use medical terminology. If the subject's symptoms and signs can be summarized under a common etiology, a diagnostic term should be recorded whenever possible. Except for disease progression-related indicators, all clinical events and clinically significant laboratory adverse reactions can be managed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Treatment-emergent adverse reactions will be recorded by the investigator.

9.3.3 Collection and Reporting of SAEs

All SAEs occurring from the time the subject signs informed consent until 4 weeks after completion of the study device, regardless of cause or relationship to the study device, must be reported using an SAE report form. If an SAE occurs, the investigator shall immediately take appropriate treatment measures to ensure subject safety, and report to the ethics committee of the corresponding clinical trial center and the Medical Administration Division of the National Health Commission within 24 hours, and promptly report to the lead unit ethics committee. The initial report should include, as much as possible: source of report, study device name, SAE name, onset time, severity, duration, relationship to the study device, actions taken, and outcome.

9.3.4 Pregnancy

Females of childbearing potential should use effective contraceptive methods during the period specified in the study. The methods should minimize the possibility of contraceptive failure. Before recruiting females of childbearing potential, the investigator must inform women of childbearing age about the importance of avoiding pregnancy during participation in the study and the potential risks of unintended pregnancy. Subjects must sign informed consent to confirm that these issues have been discussed and are fully understood.

Pregnancy testing requirements: All females of childbearing potential must have a negative serum pregnancy test at screening and at baseline/Day -1. Additionally, the investigator should inform all females of childbearing potential that they should report immediately if they suspect they may be pregnant (e.g., missed or delayed menstruation) at any time during the trial.

Pregnancy reporting: If a subject becomes pregnant or is suspected of being pregnant during the study, it should be recorded and reported accordingly.

9.3.5 Severity Grading of AEs

The investigator will grade severity using the five-point scale defined in NCI CTCAE version 5.0:

- Grade 1, mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2, moderate; limiting age-appropriate instrumental activities of daily living (e.g., cooking, shopping, using the phone).
- Grade 3, severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing, eating, toileting, taking medication, but not bedridden).
- Grade 4, life-threatening; urgent intervention indicated.
- Grade 5, death related to AE.

9.3.6 Other Responsibilities of the Investigator during SAE Follow-up

The investigator should perform appropriate examinations and treatment based on clinical judgment for SAEs, including necessary clinical laboratory tests, physical examinations, etc. Any results of examinations or other updated SAE-related

information must be reported in a follow-up report. The timeline and process for follow-up reports are the same as for the initial report.

10. TRIAL TERMINATION / SUSPENSION CRITERIA

10.1 The sponsor has the right to terminate/suspend this trial. Before terminating/suspending a clinical trial, the sponsor shall notify the investigator and the ethics committee and state the reasons. After early termination/suspension, the study may only be resumed after approval by the ethics committee.

10.2 Termination/suspension requested by the ethics committee.

11. CONDITIONS FOR CLOSURE OF THE CLINICAL TRIAL

The trial will be considered ended when all subjects meet the following conditions:

1. All subjects have completed the follow-up specified in the study;
2. Or all subjects have died, been lost to follow-up, or withdrawn informed consent.

12. DATA MANAGEMENT

12.1 Data Management

1. The investigator must ensure that the data are authentic, complete, and accurate.
2. Any corrections to trial records must be made by drawing a single line through the error, inserting the corrected data next to it, stating the reason, and signing and dating by the investigator. Erasure or overwriting of original records is not permitted.
3. Laboratory tests must be complete.

12.2 Data Recording and Document Preservation

Subject data on the case report form shall be recorded using subject codes; subjects can only be identified by their subject code or initials of their name.

This trial uses an online EDC system for data management. From data entry, source data verification, and query resolution to database locking and export, after confirming that there are no questions, all parties sign the database lock application form, and the data administrator locks the database. After database lock, the data administrator exports the analysis database and submits it to the statistician for statistical analysis. Locked data cannot be edited further. Issues discovered after database lock may be corrected in the statistical analysis program after confirmation.

13. STATISTICAL ANALYSIS

13.1 Sample Size Determination

This study is expected to be conducted at 12 domestic and international centers. The sample size is based on the composite rate of aneurysm embolization and complications. Referencing large-sample international studies and meta-analyses on aneurysm complication rates:

Bleeding and ischemic complications related to intracranial aneurysm treatment are closely associated with clinical outcomes. Therefore, this clinical study uses treatment-related postoperative complications within 1 year as the primary endpoint. Literature search results show that the rate of treatment-related complications at 1 year after flow diverter treatment is approximately 22%[26], while that for traditional interventional methods for unruptured intracranial bifurcation aneurysms is approximately 8.9%[27]. Thus, assuming a complication rate of 22.00% for flow diverter treatment and 8.9% for traditional interventional methods, the treatment effect difference is 13.1%. The two groups will be randomized 1:1, using the O'Brien-Fleming alpha spending function, with two interim analyses planned at one-third and two-thirds of the sample size. With a two-sided significance level of 0.05 and power of 80%, a total of 238 patients (119 in each group) are required. Assuming a dropout rate of 10%, the final sample size needed is 266 patients (133 in each group).

Sample size calculation formula:

$$n = \frac{\left(z_{1-\alpha/2} \sqrt{2\bar{p}(1-\bar{p})} + z_{1-\beta} \sqrt{p_1(1-p_1) + p_2(1-p_2)} \right)^2}{(p_1 - p_2)^2}$$

13.2 Definitions and Selection of Analysis Sets

Full Analysis Set (FAS): All subjects who were enrolled, received at least one dose of study drug, and had at least one efficacy assessment.

Safety Analysis Set (SS): All subjects who were enrolled, received at least one dose of study drug, and had at least one safety assessment.

Per Protocol Set (PPS): All subjects in the FAS who completed protocol-specified treatment without serious protocol violations.

13.3 Statistical Methods

Baseline data and efficacy analyses will be performed based on the Full Analysis Set (FAS); safety analyses will be performed based on the Safety Analysis Set (SAS). All statistical analyses will use two-sided tests, with $P < 0.05$ considered statistically significant.

Baseline characteristics description: Based on the FAS, descriptive summaries of subject baseline characteristics will be performed. Chi-square tests will be used for categorical data, and t-tests or non-parametric tests for continuous data for between-group comparisons.

Primary evaluation index: According to the intention-to-treat (ITT) principle, the chi-square test will be used to compare differences between the two treatment arms for FAS data. Cox proportional hazards models will be used to calculate the hazard ratio (HR) and its 95% confidence interval for the composite event of significant aneurysm recurrence, any stroke, and all-cause death within 1 year after surgery between the two treatment arms.

Secondary evaluation indices: Analyses of secondary indices will follow general statistical analysis principles. For binary indices, chi-square tests will be used to compare differences between the two treatment arms, and generalized linear regression models will be used to calculate RR and its 95% CI. For survival indices, Cox proportional hazards models will be used to calculate HR and its 95% CI between the two treatment arms.

Based on the SAS dataset, for most safety endpoints, Cox proportional hazards models will be used to calculate and compare the hazard ratio (HR) between the two treatment arms, or Poisson regression or negative binomial regression, which are more suitable for rare events, will be used.

13.4 Statistical Software and General Requirements

- All statistical analyses will be performed using R 4.4.3 (or higher).
- Continuous data will be described using mean, standard deviation, median, minimum, maximum.
- Categorical data will be described using frequencies and percentages.
- The primary index of this study will be statistically tested.

14. TRIAL MANAGEMENT

14.1 Compliance with GCP Requirements

Management and implementation of GCP:

1. Investigators shall use standard operating procedures for quality control and quality assurance of the clinical trial.
2. Source documents must comply with Chinese GCP requirements.
3. Laboratory test results must be accurate and reliable.
4. All observed results and findings must be verified to ensure data reliability.
5. Establish a complete trial organizational structure and clarify responsibilities at each level.
6. The principal investigator is responsible for overall quality control, implementing responsibilities at each level.
7. The principal investigator is responsible for designing the protocol and informed consent form, and will write the final trial report after completion.

8. Before the trial, the trial team will organize all participants to study the protocol; all trial personnel must undergo training.
9. Physicians and nurses participating in the trial must strictly adhere to the protocol and follow procedures without arbitrary changes.
10. Designated statisticians will be responsible for comprehensive statistical processing of the data.

14.2 Protection of Subject Privacy

All subject data during the trial will be entered into a computer for confidential storage and analysis. When necessary, relevant authorities may review the records to verify the authenticity, accuracy, and completeness of the data. The data obtained from the trial may also be published in academic journals, but the subjects' names will not be disclosed, and subjects' privacy will be kept confidential.

Additional precautions will be taken to ensure confidentiality of documents and to prevent identification of subjects through genetic data. However, in special circumstances, certain personnel may have access to a subject's genetic data and personal identifiers. For example, in the event of a medical emergency, the sponsor, its representative physician, or the investigator may be aware of the subject's identifier and have access to that subject's genetic data. Additionally, relevant regulatory authorities may require access to relevant documents.

14.3 Handling of Issues Arising During the Trial

1. Protocol amendments: After approval by the ethics committee, if amendment is required, a "Protocol Amendment Explanation" shall be prepared and signed by the principal investigator. The protocol may only be amended after consultation and agreement between the investigator and the drug/device applicant.
2. After amendment, the protocol must be submitted to the ethics committee for approval before implementation.
3. No person participating in the trial may deviate from the protocol. If a protocol deviation occurs, a written explanation must be provided to the sponsor, who then has the right to decide whether to continue the trial.
4. If a subject has a minor protocol deviation, the investigator shall promptly notify the drug/device applicant and jointly discuss how to handle the deviation and whether the subject should be considered withdrawn. Minor deviations that do not affect subject safety or the integrity of the protocol are termed minor protocol deviations.
5. Any adverse event (AE) or serious adverse event (SAE) occurring during the trial will be reported and managed according to the requirements of this protocol and relevant regulations.

14.4 Quality Control and Quality Assurance

14.4.1 Quality Assurance:

The sponsor and all cooperating units entrusted with all or part of the responsibilities and tasks related to this study (including CRO, SMO, statistical units, clinical centers,

etc.) shall establish their own quality assurance systems, fulfill their respective responsibilities, strictly follow the clinical trial protocol, and adopt corresponding standard operating procedures to ensure the implementation of the clinical trial quality control and quality assurance system.

14.4.2 Quality Assurance during the Clinical Trial Process

Before the trial starts, investigators shall receive training on the protocol so that research personnel fully understand the protocol and the specific meanings of its indicators. Quality control personnel shall verify the basic conditions of the clinical trial to ensure that the trial conditions meet the protocol requirements. During the trial, investigators shall carefully perform clinical operations according to the institutional SOPs and protocol requirements, and make records truly, promptly, completely, and normatively. Quality control personnel shall perform quality checks on the trial process and corresponding source records. After the trial ends, the research unit shall organize the corresponding project documents, which shall be archived and preserved after verification by quality control personnel. When non-conformities are identified, the investigator and unit head shall be promptly notified for correction, and the correction shall be tracked.

14.5 Expected Timeline and Completion Date

- June 2025 to December 2027: Complete patient enrollment, 12-month follow-up, and data collection.
- January 2028 to December 2028: Complete data analysis, manuscript writing, and publication.

14.6 Sponsor Responsibilities

The sponsor is responsible for initiating, applying for, and organizing this clinical trial, and providing trial funding. The sponsor selects the institutions and investigators for the clinical trial and verifies their qualifications and conditions to ensure completion of the trial.

14.6.1 Investigator Responsibilities

The study will be conducted in accordance with the ethical, moral, and scientific principles of the Declaration of Helsinki and Chinese GCP, as well as the protocol design and provisions. The investigator is responsible for making medical decisions related to the clinical trial and ensuring that subjects receive timely treatment for AEs during the trial. The investigator shall be aware of the procedures and requirements for reporting SAEs and shall record and report these events accordingly. The investigator shall accurately, completely, promptly, and lawfully enter data into the eCRF, accept monitoring or auditing by monitors or auditors dispatched by the sponsor or CRO, and accept inspections by drug regulatory authorities to ensure the quality of the clinical trial.

14.6.2 Method of Publication of Study Data by the Sponsor

The sponsor has exclusive rights to the study data. Unless written consent is obtained from the sponsor, no individual may publish a manuscript before the final report of the multicenter study is completed. The sponsor has final decision-making authority regarding manuscripts and publication.

Data management: Subject source data will not be sent outside.

14.6.3 Regarding the collection, acquisition, trading, export, and cross-border transfer of human genetic resources, compliance with the "Regulations of the People's Republic of China on the Management of Human Genetic Resources" (State Council Decree No. 717, May 2019) is required.

15. ETHICAL CONSIDERATIONS RELATED TO THE TRIAL

15.1 Ethics Committee

Before the study begins, the investigator shall submit the protocol, informed consent form, and other documents to the ethics committee for approval. Any amendments to the protocol must be re-approved by the ethics committee.

15.2 Informed Consent

Qualified investigators must explain in detail the nature, purpose, relevant procedures, expected duration, potential risks and benefits, and any possible discomforts of the trial to each subject during the informed consent process. Each subject must be informed that participation in the trial is voluntary, that they may withdraw from the trial or revoke informed consent at any time, and that this will not affect their subsequent treatment or relationship with the treating physician.

The informed consent form should be written in a standard format and use lay language as much as possible. Each informed consent form must include all the relevant content above, including a voluntary statement. The informed consent form must be submitted to the ethics committee for approval.

After explaining the basic content of the trial and after the investigator is confident that each potential subject understands the purpose of the trial, each subject who will participate in the trial should be asked to sign and date the informed consent form. Subjects should read and consider the statement before signing and dating, and should receive a copy of the signed informed consent form. A subject cannot enter the trial without obtaining informed consent and signing the informed consent form.

15.3 Other

When a subject is unable to participate in the informed consent process independently, a reliable impartial witness/legal representative must be present throughout the informed consent process. The selection of the impartial witness/legal representative must not infringe on the subject's right to confidentiality. After verbal

consent from the subject, the impartial witness/legal representative shall sign and date the informed consent form to certify that the information was accurately conveyed.

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Clinical Trial Protocol Confirmation Signature Page

Traditional approach versus Flow Diverter for unruptured intracranial wide-neck bifurcation aneurysms: a prospective international multicenter randomized controlled study (FD-BWA study)

Principal Investigator's Agreement to the Protocol:

I have carefully read this protocol. I agree with all the necessary information included in the protocol for conducting the study, and I agree to conduct the study as described. I understand that the trial shall not be initiated without the approval of the Ethics Committee and shall be conducted in full compliance with the regulations of my institution.

Principal Investigator Signature: _____ Date: _____
