Protocol Number: 2023ZD0504402

Clinical Trial Protocol

Arch-Clamping Technique under Mild Hypothermia in Treating with Acute Type A Aortic Dissection: Study Protocol for a Multicenter, Three-arm, Open-label, Randomized, Parallel-controlled Trial

Sponsors: Beijing Anzhen Hospital, Capital Medical University

Collaborators: First Affiliated Hospital of Air Force Medical University

Kunming Yan'an Hospital

Xiangya Hospital, Central South University

West China Hospital, Sichuan University

Guangzhou First People's Hospital

First Affiliated Hospital of Xi'an Jiaotong University

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CONTENTS

ABBREVIATION LIST

Abbreviation	Full Name
ATAAD	Acute Type A Aortic Dissection
TAR+FET	Total Arch Replacement Combined with Frozen Elephant Trunk Implantation
CPB	Cardiopulmonary Bypass
EACTS/STS	European Association for Cardio-Thoracic Surgery/The Society of Thoracic Surgeons
CTA	Computed Tomography Angiography
ICU	Intensive Care Unit
RRT	Renal Replacement Therapy
AKI	Acute Kidney Injury
KDIGO	Kidney Disease Improving Global Outcomes Criteria
ASIA	American Spinal Cord Injury Association
BMI	Body Mass Index
BSA	Body Surface Area
ECG	Electrocardiogram
LCCA	Left Common Carotid Artery
LSCA	Left Subclavian Artery
FAS	Full Analysis Set
PPS	Per Protocol Set
EDC	Electronic Data Capture
CRF	Case Report Form

PROTOCOL SUMMARY

Study Title	Arch-Clamping Technique under Mild Hypothermia in Treating with Acute Type A Aortic Dissection: Study Protocol for a Multicenter, Three-arm, Open-label, Randomized, Parallel-controlled Trial
Study Objectives	(1) To evaluate the validity and safety of arch-clamping technique under mild hypothermia for acute type A aortic dissection (ATAAD) using Sun's procedure with bilateral anterograde cerebral perfusion (bACP) as the comparator. (2) To evaluate the validity and safety of arch-clamping technique under mild hypothermia for ATAAD using arch-clamping technique under moderate hypothermia as the comparator.
Study Design	Multicenter, Three-arm, Open-label, Parallel-controlled, Randomized, Superiority Study
Sample Size	This study plans to include 306 participants, divided into three groups of 102 participants each in a 1:1:1 ratio.
Inclusion Criteria	(1) Computed tomography angiography (CTA) confirmed as ATAAD according to the 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease; (2) Adult patients (18-70 years) weighing 50-120 kg; (3) Time interval between the onset of symptoms and operation is less than 14 days; (4) Indications for total aortic arch replacement are available; (5) Signed informed consent and availability for follow-up.
Exclusion Criteria	(1) History of chronic renal failure, hepatocirrhosis, and hepatic insufficiency; (2) Severe gastrointestinal complications of non-aortic dissection, such as mesenteric ischemia, gastrointestinal bleeding, hepatopancreaticobiliary dysfunction, and intestinal obstruction;

	(3) History of severe cerebral infarction (with cerebral infarction sequels); (4) Preoperative intubation or unconsciousness; (5) Inflammatory aortic diseases, such as Takayasu arteritis and Behçet's disease etc; (6) History of infectious aortic diseases; (7) History of cardiac and aortic surgery; (8) History of malignancy or previous radiotherapy; (9) Pregnant or feeding women, or anyone planning to reproduce during the test period; (10) Without informed consent signature; (11) Participating in any other clinical trial; (12) Having other causes not eligible for operation.
Study Period	June 2025 to June 2027
Study Methods	The study is a multicenter, three-arm, open-label, randomized, parallel-controlled trial, which plans to enroll 306 participants diagnosed with acute type A aortic dissection (ATAAD) from 7 hospitals in China. All patients receive total arch replacement (TAR) combined with frozen elephant trunk (FET) implantation and are randomized to Group 1 (arch-clamping technique under mild hypothermia), Group 2 (arch-clamping technique under moderate hypothermia) and Group 3 (Sun’s procedure using bilateral antegrade cerebral perfusion) in the ratio of 1:1:1. After a 1-year follow-up, the validity and safety of the mild hypothermic arch-clamping technique for ATAAD is evaluated via the incidence of major adverse events including death, renal replacement therapy, stroke, and paraplegia, as well as times of circulatory arrest, cardiopulmonary bypass, and mechanical ventilation, and length of stay.

Outcome Measures	1. Primary Outcome Measures (1) Major adverse events include death, renal replacement therapy, stroke, and paraplegia 2. Secondary Outcome Measures (1) Circulatory arrest time (2) Cardiopulmonary bypass time (3) Mechanical ventilation time (4) Length of ICU stay

PRINCIPAL INVESTIGATORS

Name	Institution	Title
Hai-Sheng Chen	Guangzhou First People's Hospital	Chief Physician
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Note: Investigators are listed alphabetically by pinyin. Any changes in participating centers will be documented separately and will not require protocol amendment. *FMMU*, The Fourth Military Medical University

BACKGROUND

Acute type A aortic dissection (ATAAD) is a life-threatening cardiovascular disease with increasing death risk of 1-2% per hour after the onset of symptoms and a 48-hour mortality up to 50%. Surgical repair promptly can save patients' lives, but accompanied with high mortality and morbidities. Postoperative complications such as stroke, spinal cord injury and acute renal failure seriously impact the short- and long-term prognosis of the patients.

Total arch replacement (TAR) combined with frozen elephant trunk (FET) implantation is considered as the effective approach to avoid chronic complications and facilitate future endovascular or reintervention, which is progressively used for the treatment of a variety of pathologies involving the aortic arch and descending aorta. The adjunctive techniques of the procedure include moderate hypothermic circulatory arrest (MHCA) to decrease the core temperature and organic metabolism and selective antegrade cerebral perfusion to protect the brain [2-5]. However, hypothermia prolongs the cooling and rewarming phases and increases systemic inflammatory response exposure significantly; circulatory arrest increases ischemia-reperfusion risk, impairs coagulation mechanisms, and leads to different severities of

organ injury [5,6]. Therefore, reducing or avoiding circulatory arrest and elevating core temperature are key directions for optimizing surgical techniques.

Several observational studies and meta-analyses elaborated that selected antegrade cerebral perfusion reduces the risk of malperfusion and aortic thromboembolism, with lower operative mortality and major complication rates (i.e. strokes and reoperations for bleeding) compared to other arterial cannulation strategies. The EACTS/STS Guidelines for Diagnosing and Treating Acute and Chronic Syndromes of the Aortic Organ recommend that MHCA (26-28℃) deep hypothermic circulatory arrest (20-22℃) for arch surgery in ATAAD [7]. However, using unilateral or bilateral cerebral perfusion remains controversial. Several studies indicate that unilateral and bilateral cerebral perfusion are similar in preventing postoperative neurological dysfunction, while international guidelines recommend using bilateral antegrade cerebral perfusion (bACP) in cases of the prolonged circulatory arrest [7,8]. In 2019, Professor Jun-Ming Zhu and colleagues from Beijing Anzhen Hospital proposed a novel technical approach for TAR + FET procedure called arch-clamping technique to treat ATAAD. This approach is performed under MHCA (25-28℃), a FET is deployed in the descending aorta and clamped together with the autologous aorta immediately, then distal perfusion was restored via the femoral artery (Figure 1). This approach is easy to manipulate without additional assistive devices, of which the circulatory arrest time is usually limited to about 3 minutes, as well as significantly reducing the CPB duration. The early outcomes showed it was safe and effective in reducing mortality and morbidities. (Table 1) [9,10].

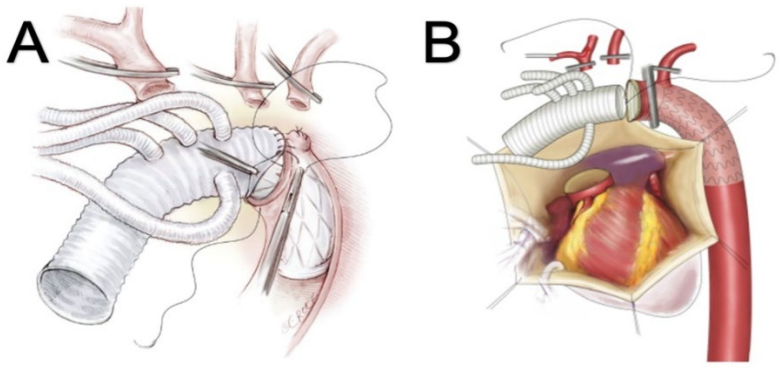

Figure 1. A: Conventional TAR + FET procedure; B: Arch-clamping technique.

Table 1. The early-outcomes between arch-clamping technique and conventional TAR + FET procedure

Variables	Arch-clamping Technique (n = 39)	Conventional TAR + FET Procedure (n = 40)	*P* value
Circulatory arrest time, (min)	4.1 ± 0.6	23 ± 8.8	0.001
Cross Clamp time, (min)	96.9 ± 4.4	127.1 ± 13.3	0.001
CPB time, (min)	158.4 ± 6.8	198.0 ± 12.6	0.001
Postoperative drainage, (ml) *	465 ± 95.5	440.0 ± 100.5	0.260
Intubation time, (h)	13.6 ± 2.2	34.1 ± 14.3	0.001
Red blood cells transfusion, (U)	4.5 ± 1.5	4.1 ± 1.3	0.210
CRRT, n (%)	1 (2.6)	8 (20)	0.029
Stroke, n (%)	1 (2.6)	2 (5)	0.571
Thirty-day death, n (%)	2 (5)	3 (7.5)	1.000

Values are presented as n (%) or mean ± standard deviation. * Postoperative 12-hour Drainage; *CPB,* Cardiopulmonary bypass; *CRRT*, Continuous renal replacement therapy.

Our team also try to elevate the core temperature of the circulatory arrest over 28℃. We compared the early outcomes of arch-clamping technique under different temperatures. The results demonstrated that the CPB duration and cross-clamp time were significantly reduced in the mild hypothermia group compared to moderate hypothermia group. Meanwhile, the mild hypothermia group has lower mortality and morbidities, especially for the incidences of stroke, spinal cord injury, and continuous renal replacement therapy (Figure 2) [11]. Our previous studies also found that using bACP as a brain protective strategy can significantly reduce the incidence of permanent neurological dysfunction [12,13]. Therefore, we hypothesize that arch-clamping technique combined mild hypothermia and bACP as a surgical bundle can be effective in minimizing the circulatory arrest time and mitigating multi-organ injury due to temperature changes and prolonged CPB duration.

In summary, we designed a multicenter randomized controlled trial to observe the 30-day and 1-year outcomes of patients with ATAAD after operation, seeking to validate the efficacy and safety of arch-clamping technique under mild hyperthermia

using bACP for the treatment of ATAAD.

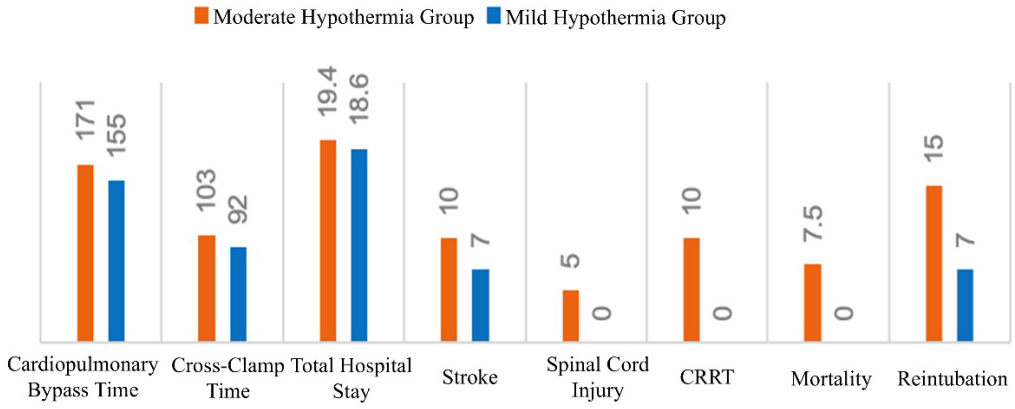

Figure 2. Postoperative outcomes of using the arch-clamp technique in treating with ATAAD at different temperatures. Cardiopulmonary bypass time and cross-clamp time were presented as minutes; Total hospital stay was presented as days; Other variables were presented as n (%). *CRRT,* Continuous renal replacement therapy.

STUDY OBJECTIVES

(1) To evaluate the validity and safety of arch-clamping technique under mild hypothermia for ATAAD using Sun's procedure with bACP as the comparator.

(2) To evaluate the validity and safety of arch-clamping technique under mild hypothermia for ATAAD using arch-clamping technique under moderate hypothermia as the comparator.

STUDY DESIGN

Summary

The study is a multicenter, three-arm, open-label, randomized, parallel-controlled trial, which plans to enroll 306 participants diagnosed with ATAAD from 7 hospitals in China. All patients receive TAR + FET procedure and are randomized to Group 1 (arch-clamping technique under mild hypothermia), Group 2 (arch-clamping technique under moderate hypothermia) and Group 3 (Sun's procedure using bilateral antegrade cerebral perfusion) in the ratio of 1:1:1. After a 1-year follow-up, the validity and safety of the mild hypothermic arch-clamping technique for ATAAD is

evaluated via the incidence of major adverse events including death, renal replacement therapy (RRT), stroke, and paraplegia, as well as times of circulatory arrest, cardiopulmonary bypass, and mechanical ventilation, and length of stay.

Rationale for Study Design

(1) Prospective: Prospective design minimizes bias. Standardized enrollment criteria, methods, process, and outcome measures, clarify the causal relationship.

(2) Multicenter: Multicenter trials can enroll participants rapidly, resulting in shorter clinical trial periods, good extrapolation, and minimal bias caused by systematic errors.

(3) Three-arm: This study involves two technical optimizations: temperature change from moderate temperature to mild temperature; unilateral antegrade cerebral perfusion changed to bACP. Due to the inability to control two variables simultaneously using a two-arm design, we plan to establish three groups for a randomized controlled trial.

(4) Randomized: This trial uses randomization at each center. Each participant successfully screened has equal opportunity and is randomly assigned to Group 1 (arch-clamping technique under mild hypothermia), Group 2 (arch-clamping technique under moderate hypothermia) and Group 3 (Sun’s procedure using bilateral antegrade cerebral perfusion) in a 1:1:1 ratio without the investigator nor the participant's personal preferences influence.

(5) Open-label: The three surgical procedures differ significantly in terms of manipulation, so it is impossible to blind the researchers and participants.

(6) Parallel-controlled: Sun’s procedure as a TAR+FET technique, is the standard surgical treatment for ATAAD.

Subject Selection

Inclusion Criteria

(1) Computed tomography angiography (CTA) confirmed as ATAAD according

to the 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease; Diagnosis consistent with ATAAD confirmed by aortic CTA;

(2) Adult patients (18-70 years) weighing 50-120 kg;

(3) Time interval between the onset of symptoms and operation is less than 14 days;

(4) Indications for total aortic arch replacement are available;

(5) Signed informed consent and availability for follow-up.

Exclusion Criteria

(1) History of chronic renal failure, hepatocirrhosis, and hepatic insufficiency;

(2) Severe gastrointestinal complications of non-aortic dissection, such as mesenteric ischemia, gastrointestinal bleeding, hepatopancreaticobiliary dysfunction, and intestinal obstruction;

(3) History of severe cerebral infarction (with cerebral infarction sequels);

(4) Preoperative intubation or unconsciousness;

(5) Inflammatory aortic diseases, such as Takayasu arteritis and Behçet's disease etc;

(6) History of infectious aortic diseases;

(7) History of cardiac and aortic surgery;

(8) History of malignancy or previous radiotherapy;

(9) Pregnant or feeding women, or anyone planning to reproduce during the test period;

(10) Without informed consent signature;

(11) Participating in any other clinical trial;

(12) Having other causes not eligible for operation.

Criteria and Process for Participant Withdrawal

All participants who sign the informed consent and qualify for the trial, regardless of time and reason for withdrawal, will be considered early withdrawals if

they have not completed the observation period.

(1) Withdrawal by investigators decision.

- Serious adverse events occurred, and the investigators determine that the trial should be terminated.
- Participants suffering from complications and special physiological changes that render them unsuitable to continue the trial.
- Poor compliance.

(2) Voluntary Withdrawal.

- Participant is unwilling or unable to continue participation for any reason and requests withdrawal.
- Participant does not explicitly request withdrawal but refuses further treatment and/or follow-up.

(3) Handling of Early Withdrawal

- All early withdrawals must be documented in the case report form, including completion of the study summary page and reason for withdrawal. After early withdrawal, the investigator should make every effort to contact the subject, inquire about the reason for withdrawal, and complete as many assessment items as possible.

Criteria and Procedures for Study Termination

The clinical study should be suspended or terminated by the medical institution under the following circumstances, with full consideration of subject safety:

(1) Violation of laws, regulations, or rules;

(2) Breach of ethical principles or scientific integrity;

(3) Discovery of serious quality defects in related drugs or medical devices during the study;

(4) Identification of significant safety risks in the clinical study;

(5) Existence of commercial bribery or other improper interests;

(6) Misuse of research funds.

Investigators may apply to suspend or terminate the clinical study. Applications for suspension or termination must be reported to the clinical research management department with stated reasons. The medical institution will make decision in accordance with the full-process management system for clinical research. For enrolled subjects, the study treatment will be discontinued, and protocol-specified follow-up visits will be completed. Investigators will provide routine clinical care as needed according to each subject's actual situation.

EVALUATION METHODS

Primary Outcome Measures

Major adverse events include death, RRT, stroke, and paraplegia. The definitions, assessment methods, and observation time points for each indicator are as follows:

(1) Mortality

Definition: Death occurring within 30 days postoperatively or before final hospital discharge, including transfer to other acute care facilities.

Assessment Method: For in-hospital events, clinical death is declared when the patient's electrocardiogram shows asystole and declared clinical death. For post-discharge events, death confirmed by telephone follow-up.

Observation Time Points: Discharge day / postoperative 30 days and 12 months.

(2) Renal Replacement Therapy

Definition: Use of artificial methods such as hemodialysis to replace renal function for removal of metabolic waste and regulation of fluid and electrolyte balance in the event of severe renal failure.

Assessment Method: Indications include volume overload unresponsive to diuretics; severe hyperkalemia (>6.5 mmol/L) or rapidly rising potassium with cardiotoxicity; severe metabolic acidosis (pH <7.1); acute kidney injury (AKI) patients unable to tolerate fluid balance and metabolic fluctuations; refractory fluid overload, septic shock, severe electrolyte or acid-base imbalance, acute hepatic failure, severe tumor lysis syndrome, heat stroke, etc. AKI diagnosis and grading are

based on the KDIGO (Kidney Disease: Improving Global Outcomes) criteria (Table 3).

Table 3 Definition and Grading Criteria of Acute Kidney Injury

Acute Kidney Injury	
Definition	**Meets any one of the following:** **a.** Increase in serum creatinine ≥0.3mg/dL (26.5μmol/L) within 48 hours; **b.** Increase in serum creatinine to ≥1.5 times baseline, known or presumed to have occurred within the prior 7 days; **c.** Urine output <0.5 mL/kg/h for 6 hours.
Grading Criteria	**Stage 1**: Serum creatinine rises by an absolute value of ≥0.3 mg/dL (26.5 μmol/L), or increases by ≥0.5 times but less than 1 time relative to baseline; or urine output <0.5 mL/kg/h for ≥6 hours but <12 hours.
	Stage 2: Serum creatinine increases by ≥1 time but less than 2 times relative to baseline; or urine output <0.5 mL/kg/h for ≥12 hours but <24 hours.
	Stage 3: Any of the following: **a.** Serum creatinine ≥4.0 mg/dL (353.6 μmol/L); **b.** Serum creatinine increases by ≥2 times relative to baseline; **c.** Urine output <0.3 mL/kg/h for ≥24 hours; **d.** Anuria for ≥12 hours; **e.** Initiation of renal replacement therapy.

* Due to intraoperative management interventions (such as mannitol administration), hourly urine output on the day of ICU admission will not be included in the assessment criteria for acute kidney injury.

Observation Time Points: Postoperative 1 to 3 days, and discharge day / postoperative 30 days.

(3) Stroke

Definition: Acute onset of new focal or global neurological deficit.

Assessment Method: At least one of the following: altered level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, aphasia or language disturbance, hemianopia, amaurosis, or other focal/global neurological deficits lasting ≥24 hours; or neurological deficit resulting in death. All events must be confirmed by imaging and corresponding reports.

Observation Time Points: Postoperative 1 to 3 days, and discharge day / postoperative 30 days.

(4) Paraplegia

Definition: New-onset ischemic spinal cord injury postoperatively, resulting in motor and sensory dysfunction of both lower limbs below the level of injury, with corresponding neurological signs.

Assessment Method: Graded according to the American Spinal Injury Association (ASIA) Impairment Scale with stroke excluded (**Table 4**).

Table 4. American Spinal Injury Association (ASIA) Impairment Scale

Grade	Clinical Manifestations
A (Complete injury)	No sensory or motor function preserved.
B (Incomplete injury)	Sensory function is preserved below the neurological level, including the sacral segments, but no motor function is preserved.
C (Incomplete injury)	Motor function is preserved below the neurological level, but more than half of key muscles have a muscle grade less than 3.
D (Incomplete injury)	Motor function is preserved below the neurological level, and at least half of key muscles have a muscle grade of 3 or greater.
E (Normal)	Sensory and motor functions are normal.

Note: Muscle strength grading: 0-No movement in the lower limbs; 1-Lower limb movement cannot overcome gravity; 2-Limb movement can overcome gravity; 3-Able to stand with assistance; 4-Able to walk with assistance; 5-Normal.

Observation Time Points: Postoperative 1 to 3 days, and discharge day / postoperative 30 days.

Secondary Outcome Measures

(1) Circulatory Arrest Time

Definition: time interval between ceasing and restarting cardiopulmonary bypass when core temperature reaches moderate hypothermia.

Assessment Method: According to the cardiopulmonary bypass record sheet.

Observation Time Point: Operation day.

(2) Cardiopulmonary Bypass Time

Definition: start-to-end time of cardiopulmonary bypass to complete aortic repair.

Assessment Method: According to the cardiopulmonary bypass record sheet.

Observation Time Point: Operation day.

(3) Duration of Mechanical Ventilation

Definition: time interval between mechanical ventilation and extubation after operation.

Assessment Method: According to the intensive care unit record sheet.

Observation Time Point: Discharge day / postoperative 30 days.

(4) Length of ICU stay

Definition: time interval from ICU admission to transfer or death.

Assessment Method: According to the intensive care unit record sheet.

Observation Time Point: Discharge day / postoperative 30 days.

Interventions

Arch-Clamping Technique under Mild Hypothermia

This procedure is performed under mild hypothermia. The branch arteries of the arch are reconstructed using the side arms of a Y-shaped graft, which allows bilateral antegrade cerebral perfusion (bACP) through the right axillary artery. A FET is deployed in the descending aorta and clamped together with the autologous aorta immediately, then distal perfusion is restored through the femoral artery. After the proximal procedures is completed, the distal anastomosis is performed in an end-to-end fashion. Finally, the main trunk of the Y-shaped graft is anastomosed to the proximal grafts.

Arch-Clamping Technique under Moderate Hypothermia

This procedure is performed under moderate hypothermia. The branch arteries of the arch are reconstructed using the side arms of a Y-shaped graft, which allow bACP through the right axillary artery. A FET is deployed in the descending aorta and clamped together with the autologous aorta immediately, then distal perfusion is restored through the femoral artery. After the proximal procedures is completed, the distal anastomosis is performed in an end-to-end fashion. Finally, the main trunk of

the Y-shaped graft is anastomosed to the proximal grafts.

Sun's Procedure using bACP

Sun's procedure is performed using bACP under MHCA, which involves FET deployment in the descending aorta followed by total arch replacement with a four-branched vascular graft. Deployment of the FET and suture of distal anastomosis are completed during bACP. MHCA is terminated and distal reperfusion is initiated once the distal anastomosis is completed, and the left carotid artery is reconstructed first (after which bACP is stopped, rewarming is started and the brain is perfused bilaterally). The root or valve procedures and some concomitant operations, if indicated, are performed during the cooling phase.

Study Procedures

Study Flowchart

Point / Items	Point 1	Point 2	Point 3	Point 4	Point 5	Point 6	Point 7
	Enrollment	Treatment				Follow-up	
	Emergency Admission	Operation Day	Post-op Day 1	Post-op Day 2-3	Discharge/30 ±7 Days	6 months ±7 days	12 months ±7 days
Informed Consent	X						
Medical History & Demographics	X						
Symptoms & Physical Examination	X		X	X	X		
Laboratorial Biomarkers							
Hemogram	X		X	X	X	X	X
Coagulation	X		X	X	X	X	X
Myocardial Injury	X		X	X	X	X	X
BNP	X		X	X	X	X	X
Liver Function	X		X	X	X	X	X
Renal Function	X		X	X	X	X	X
Electrocardiogram	X				X	X	X
Imaging Index	X				X	X	X
Primary Outcome *							
MAEs			X	X	X	X	X
Secondary Outcomes					X		
Circulatory Arrest Time		X					
CPB Time		X					
Duration of MV			X	X	X		
Length of ICU Stay			X	X	X		

***** Primary Outcome which include death, renal replacement therapy, stroke, and paraplegia; MAEs, Major adverse events; RRT: Renal replacement therapy; CPB, Cardiopulmonary Bypass; MV: Mechanical Ventilation.

Study-Related Assessments

Medical History and General Information

(1) Demographics: Age, sex, height, weight, body mass index (BMI), body surface area (BSA).

(2) Medical History: History of hypertension, coronary artery disease and treatment, diabetes mellitus and treatment, neurological complications and treatment, chronic obstructive pulmonary disease, chronic renal failure and treatment, thyroid dysfunction, peripheral vascular disease, history of cirrhosis or gastrointestinal bleeding, family history of hereditary aortic diseases (Marfan syndrome, Loeys-Dietz

syndrome, vascular Ehlers-Danlos syndrome, familial thoracic aortic aneurysm and dissection, etc).

Symptoms and Physical Examination

(1) Symptoms: Location and quality of pain; concomitant symptoms such as dizziness, syncope, amaurosis, numbness or motor impairment of the limbs, abdominal distension, melena, or hematochezia.

(2) Physical Signs: Presence or absence of femoral and dorsalis pedis artery pulses; presence or absence of bowel sounds (noting hyperactive or absent sounds); color and skin temperature of the extremities.

Preoperative Laboratorial Tests

(1) Complete blood count: Hemoglobin, white blood cell count, neutrophil count, neutrophil percentage, C-reactive protein, platelet count;

(2) Biomarkers of coagulation function: D-dimer, fibrinogen;

(3) Biomarkers of myocardial injury: Myoglobin, troponin, creatine kinase-MB, creatine kinase, lactate dehydrogenase, B-type natriuretic peptide;

(4) Biomarkers of liver function: Albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin.

(5) Biomarkers of renal function: Serum creatinine, creatinine clearance rate, uric acid, cystatin C;

(6) Arterial blood gas analysis: PaO_2, $PaCO_2$, arterial oxygen saturation, arterial potassium, arterial lactate.

Preoperative Electrocardiogram and Imaging Indicators

(1) Electrocardiogram (ECG): Assess for signs of myocardial ischemia or infarction.

(2) Echocardiography

- Measure diameters of the aortic sinus, ascending aorta, arch, descending

artery, brachiocephalic artery, left common carotid artery (LCCA), and left subclavian artery (LSCA);

- Assess primary tear location and size, and involvement of the aortic sinus, ascending aorta, arch, descending aorta, brachiocephalic artery, LCCA, LSCA, and coronary arteries;
- Assess anatomic mutations of the aorta and its branches, such as aortic arch anomalies, coarctation, common origin of brachiocephalic and LCCA, aberrant subclavian artery, abnormal origin of vertebral artery, branch artery stenosis or tortuosity;
- Assess cardiac morphology and function: Ventricular sizes and motion abnormality;
- Assess aortic valve morphology and function: leaflet prolapse, regurgitation (degree, regurgitant neck, regurgitant area).

(3) CTA

- Measure the diameters of the aortic sinus, ascending aorta, arch, descending aorta, abdominal aorta (proximal and distal regions), and Vital abdominal arteries including celiac trunk artery, superior mesenteric artery, and renal arteries;
- Assess the involvement of dissection and entry tears in the aortic sinus, ascending aorta, arch, proximal and distal arch, descending thoracic aorta, abdominal aorta (proximal and distal), brachiocephalic artery, left common carotid artery, and left subclavian artery;
- Assess anatomic variations of the aorta and its branch vessels, such as aortic arch anomalies, coarctation, common origin of the brachiocephalic and left common carotid arteries, aberrant subclavian artery, abnormal origin of the vertebral artery, branch artery stenosis or tortuosity, and severe ischemia of the aorta or its branches.

ECG and Imaging at Discharge / Postoperative Day 30, 6 Months, and 12

Months

(1) ECG: Assess for myocardial ischemia or infarction.

(2) Echocardiography

- Measure diameters including the aortic sinus, ascending aorta, arch, descending aorta, brachiocephalic artery, LCCA, and LSCA;
- Assess cardiac morphology and function: Ventricular sizes and motion abnormality;
- Assess aortic valve morphology and function: Leaflet prolapse, regurgitation (degree, regurgitant neck, regurgitant area), presence of paravalvular or anastomotic leaks.

(3) CTA

- Measure the diameters of the aortic sinus, ascending aorta, arch, descending aorta, abdominal aorta (proximal and distal regions), and Vital abdominal arteries including celiac trunk artery, superior mesenteric artery, and renal arteries;
- Assess for anastomotic leak, pseudoaneurysm formation, or prosthetic graft stenosis.

Laboratorial Tests on Postoperative Day 1

(1) Complete blood count: Hemoglobin, white blood cell count, neutrophil count, neutrophil percentage, C-reactive protein, platelet count;

(2) Biomarkers of coagulation function: D-dimer, fibrinogen;

(3) Biomarkers of myocardial injury: Myoglobin, troponin, creatine kinase-MB, creatine kinase, lactate dehydrogenase, B-type natriuretic peptide;

(4) Biomarkers of liver function: Albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin.

(5) Biomarkers of renal function: Serum creatinine, creatinine clearance rate, uric acid, cystatin C;

(6) Arterial blood gas analysis: PaO_2, $PaCO_2$, arterial oxygen saturation, arterial

potassium, arterial lactate.

Laboratorial Tests on Postoperative Days 2-3 and Discharge / Postoperative 30 Days (±7 days)

(1) Complete blood count: Hemoglobin, white blood cell count, neutrophil count, neutrophil percentage, C-reactive protein, platelet count;

(2) Biomarkers of coagulation function: D-dimer, fibrinogen;

(3) Myocardial injury markers: Myoglobin, troponin, B-type natriuretic peptide;

(4) Biomarkers of liver function: Albumin, alanine aminotransferase, aspartate aminotransferase;

(5) Biomarkers of renal function: Serum creatinine, creatinine clearance rate, uric acid, cystatin C.

Laboratorial Tests at Postoperative 6 Months (±7 days) and 12 Months (±7 days)

(1) Complete blood count: Hemoglobin, white blood cell count, neutrophil count, neutrophil percentage, C-reactive protein, platelet count;

(2) Biomarkers of coagulation function: D-dimer, fibrinogen;

(3) Myocardial injury markers: Myoglobin, troponin, B-type natriuretic peptide;

(4) Biomarkers of liver function: Albumin, alanine aminotransferase, aspartate aminotransferase;

(5) Biomarkers of renal function: Serum creatinine, creatinine clearance rate, uric acid, cystatin C.

Study Implementation

Visit Schedule and Procedures

This study comprises 7 visit points, with the specific content of each point as follows:

Visit 1: Emergency Admission

(1) Obtain signed informed consent from the subject.

(2) Collect medical history and general information.

(3) Collect symptoms and physical examination findings.

(4) Collect laboratory tests including complete blood count, liver and renal function, etc.

(5) Collect ECG and imaging data.

(6) Verify inclusion and exclusion criteria. Eligible subjects are enrolled and assigned a randomization number, and randomized to Experimental Group 1, Experimental Group 2, or Control Group.

Visit 2: Operation Day

(1) All Subjects undergo TAR+FET procedure.

(2) For subjects in the experimental groups undergo aortic repair using mild or moderate hypothermic aortic-clamping technique with bACP; for control group subjects, undergo aortic repair using Sun's procedure with bACP.

(3) Record surgical details, including cross-clamping time, CPB time, circulatory arrest time, and type and volume of intraoperative blood transfusion.

- Concomitant procedures: coronary artery bypass grafting, valve surgery, other procedures (branch arterial bypass, aortic sinus procedures).
- Cross-clamping clamping time: Time interval between ceasing and restarting cardiopulmonary bypass when core temperature reaches moderate hypothermia.
- CPB time: Start-to-end time of cardiopulmonary bypass to complete aortic repair.
- Circulatory arrest time: from cessation to resumption of circulation.
- Type and volume of intraoperative transfusion of red blood cells, platelets, plasma, cryoprecipitate.

Visit 3: Postoperative Day 1

(1) Collect symptoms and physical examination findings.

(2) Collect laboratory tests, including complete blood count, biomarkers of liver and renal function, etc.

(3) Collect the occurrence of death, RRT, stroke, and paraplegia.

(4) Collect ICU parameters:

- Duration of mechanical ventilation: Time interval between mechanical ventilation and extubation after operation.
- Length ICU of stay: Time interval from ICU admission to transfer or death.

Visit 4: Postoperative Days 2-3

(1) Collect symptoms and physical examination findings.

(2) Collect laboratory tests, including complete blood count, biomarkers of liver and renal function, etc.

(3) Collect the occurrence of death, RRT, stroke, and paraplegia.

(4) Collect ICU parameters:

- Duration of mechanical ventilation: Time interval between mechanical ventilation and extubation after operation.
- Length ICU of stay: Time interval from ICU admission to transfer or death.

Visit 5: Day of Discharge/Postoperative Day 30 (±7 days)

(1) Collect symptoms and physical examination findings.

(2) Collect laboratory tests, including complete blood count, biomarkers of liver and renal function, etc.

(3) Collect the occurrence of death, RRT, stroke, and paraplegia.

(4) Collect ICU parameters:

- Duration of mechanical ventilation: Time interval between mechanical ventilation and extubation after operation.
- Length ICU of stay: Time interval from ICU admission to transfer or death.
- Collect imaging data, including CTA and echocardiography.

Visit 6: Postoperative 6 Months (±7 days)

(1) Collect symptoms and physical examination findings.

(2) Collect laboratory tests, including complete blood count, biomarkers of liver and renal function, etc.

(3) Collect imaging data, including CTA and echocardiography.

(4) Collect the occurrence of death, RRT, stroke, and paraplegia.

Visit 7: Postoperative 12 Months (±7 days)

(1) Collect symptoms and physical examination findings.

(2) Collect laboratory tests, including complete blood count, liver and renal function, etc.

(3) Collect imaging data, including CTA and echocardiography.

(4) Collect the occurrence of death, RRT, stroke, and paraplegia.

Measures to Control Bias

(1) Prospective study design: Subjects and study methods are determined prior to the start of the trial, with all relevant confounding factors included in the statistical analysis. Strict quality control is maintained throughout the study, and all cases that meet the design criteria are included in the final analysis. This approach yields higher-quality and more reliable clinical data and avoids the selection and data processing bias associated with retrospective studies.

(2) Multicenter design: Considering differences in geographic region, hospital, or physician expertise, multicenter case samples are more representative than those from a single center. In addition, multicenter design helps prevent systematic errors from a single center that could bias study results, thereby increasing the credibility of the conclusions. To minimize inter-center variability, all study-related personnel at each center will receive standardized training.

(3) Investigator training: Prior to study initiation, the principal investigators at each center will provide training on the study protocol to ensure that all investigators

are familiar with and understand the surgical procedures for each group.

(4) Standardized application of inclusion and exclusion criteria: Subjects will be screened strictly according to the protocol's inclusion and exclusion criteria, minimizing selection bias.

Statistical Considerations

Sample Size

Estimation of Total Sample Size

Sample size estimation is performed using PASS 2021 software.

This study adopts a superiority design and a fixed sequence testing strategy. The primary outcome is the incidence of composite events, which is a low-benefit endpoint. The hypotheses are as follows:

① Experimental Group 1 is superior to the control group.

② Experimental Group 1 is non-inferior to Experimental Group.

The order of hypothesis testing is ①→②. According to the *Guideline on Multiplicity in Clinical Drug Trials*, this strategy will not inflate the overall Type I error rate (FWER), and no adjustment for multiplicity is required.

Based on previous research, the incidence of composite events with mild hypothermic aortic arch clamping combined with bilateral cerebral perfusion is approximately 13.64%, with moderate hypothermic arch clamping combined with unilateral cerebral perfusion is approximately 22.67%, and with the traditional Sun’s procedure is approximately 29.63%.

For hypothesis ①, assuming the composite event rate is 13% in Experimental Group 1 and 30% in the control group, with a superiority margin set at 0, a one-sided significance level of 0.025, a power of 80%, and an allocation ratio of 1:1, at least 91 subjects are required in each group.

For hypothesis ②, assuming the composite event rate is 25% in Experimental Group 2 with a non-inferiority margin of 5%, at a one-sided significance level of 0.025, a power of 80%, and an allocation ratio of 1:1, at least 84 subjects are required

in each group.

In summary, taking the maximum required sample size above and allocating subjects in a 1:1:1 ratio among the three groups, and accounting for a 10% dropout rate, a total of 306 subjects will be enrolled in this study, with 102 subjects in each group.

Sample Size Allocation and Determination

This study will be conducted simultaneously in multiple clinical centers. In principle, the number of subjects enrolled per center will be distributed as evenly as possible to ensure adequate center representation. However, considering feasibility and the pace of enrollment, the number of subjects recruited at each participating site may be adjusted to ensure enrollment balance among centers. In any case, the final enrollment at a single center should not exceed 50% of the total sample size.

Analysis Populations

Statistical analyses will be based on clearly defined analysis populations prior to data analysis in this study:

Full Analysis Set (FAS): The set constructed according to the intention-to-treat principle, including all subjects who participated in the study and received TAR+FET treatment.

Per Protocol Set (PPS): A subset of FAS, including all subjects who completed the trial without major protocol violations.

Baseline data will be analyzed based on the FAS, and analyses of primary and secondary outcomes will be performed on both FAS and PPS.

Criteria for Subject Exclusion

FAS Exclusion Criteria

(1) Subjects who did not receive TAR+FET treatment after enrollment;

(2) Subjects with no follow-up records.

PPS Exclusion Criteria

(1) Subjects who violated selection criteria (did not meet inclusion criteria or met exclusion criteria), and such violations substantially affect efficacy or safety assessment;

(2) Subjects in Experimental Groups 1 or 2 (arch clamping combined with bilateral cerebral perfusion) who, for any reason, are switched intraoperatively to conventional TAR+FET (control group) treatment.

In addition to the above criteria, any other conditions that may affect assessment of efficacy or safety will be determined by investigator discussion on a case-by-case basis.

Statistical Methods

General Principles

(1) Descriptive statistics: For quantitative variables, the number of cases, mean, standard deviation, median, interquartile range, minimum, and maximum values will be reported. For qualitative variables, absolute and relative frequencies will be reported.

(2) Inferential statistics: Unless otherwise specified, two-sided tests will be used, and a two-sided P-value less than or equal to 0.05 will be considered statistically significant. Comparisons of quantitative data between groups will be performed by analysis of variance or rank-sum test; comparisons of qualitative data will use the chi-square test or Fisher's exact test; multicategorical or ordinal data will be analyzed using the Cochran-Mantel-Haenszel (CMH) test.

Statistical Analysis Content

Trial Completion Status

List the total and per-center numbers and proportions of screened subjects, screening failures, and the reasons for screening failures.

Calculate the numbers and proportions of subjects enrolled, who completed the trial, and who withdrew early, including reasons for withdrawal.

Summarize protocol deviations according to the type and severity.

Provide a detailed subject population breakdown in tabular form.

Present a subject disposition flowchart, including detailed reasons for screening failures.

Baseline Data

Baseline data analysis will be conducted based on the FAS.

Descriptive statistical analysis will be performed on medical history and general information, symptoms and physical examination, laboratory tests, electrocardiogram, and imaging indicators.

Primary Endpoint Analysis

Analysis of the primary endpoint will be based on both FAS and PPS.

The primary efficacy endpoint of this study is the incidence of composite events, and a superiority test will be used.

Hypotheses for test ① are as follows:

Null hypothesis: $T1 - C \geq 0$

Alternative hypothesis: $T1 - C < 0$

Where T1 is the incidence of composite events in Experimental Group 1, and C is that in the control group. The difference in composite event rates between the two groups and the 95% confidence interval will be calculated. If the upper limit of the 95% confidence interval is less than 0, superiority is established.

Hypotheses for test ② are as follows:

Null hypothesis: $T1 - T2 \geq 0.05$

Alternative hypothesis: $T1 - T2 < 0.05$

Where T1 is the incidence of composite events in Experimental Group 1, and T2 is the incidence in Experimental Group 2. The difference and 95% confidence interval

between the two groups will be calculated. If the upper limit of the 95% confidence interval is less than 0.05, non-inferiority is established.

Testing will follow the fixed sequence of ①→②; if the previous hypothesis test is met, the subsequent comparison will be performed; otherwise, further comparison will be stopped.

Secondary Endpoint Analysis

Analysis of secondary endpoints will be conducted based on both FAS and PPS.

Statistical analysis methods will follow the general principles described above.

Handling of Missing and Abnormal Values

(1) Handling of missing data: No imputation of missing data will be conducted; analysis will be based on the data actually obtained.

(2) Handling of erroneous data: Investigators shall make written corrections to erroneous data. The database can only be locked after all errors have been corrected.

(3) Handling of unreasonable data: Investigators shall make written adjustments to unreasonable data. The database can only be locked after all unreasonable data entries have been addressed.

Data Management

Selection of EDC System

An EDC (Electronic Data Capture) system will be used for data collection.

Case Report Forms

An electronic Case Report Form (eCRF) will be used for clinical trial data collection. The eCRF will be designed based on the study protocol and paper CRF to define data collection tables, the study workflow, names of data forms, and collected data items. A corresponding data collection manual will be developed, reviewed and approved by the study team before finalization. All information entered in the eCRF

must be sourced from the subject's original records.

Database Creation and Data Collection

The data manager will establish the eCRF according to the study protocol and paper CRF and will be responsible for its testing. The testing includes page design, visit period settings, order of forms and data points for each visit, and the accuracy of user-specific access permissions.

Each user will be assigned a unique username and password. Designated personnel at the study centers will enter original data into the eCRF via a secure network. Investigators are required to collect subject data in accordance with the study protocol and complete the eCRF accurately, promptly, completely, and in compliance with the data entry guidelines. The eCRF does not serve as a source document; it will generate relevant prompts and allow site personnel to modify the entries. Prior to database lock, investigators will confirm the accuracy of data entries via electronic signature.

Database Lock

The database will be locked by the data manager after joint signature by the principal investigator and the data manager on the database lock record.

Preservation and Handover of Data Management Documentation

Data management personnel shall retain relevant documentation as required and transfer the locked database and associated materials to the statistical analysis team for statistical analysis.

Risk-Benefit Analysis

Potential Risks

This project is an interventional study. According to current experience and published literature, both aortic arch clamping with bilateral cerebral perfusion (Experimental Groups 1 and 2) and conventional TAR + FET surgery (Control Group)

can safely and effectively treat ATAAD. None of these surgical techniques are expected to increase operative risk. However, it should be noted that ATAAD itself carries risks such as preoperative pericardial tamponade and vascular rupture leading to patient death, as well as loss of surgical indications due to poor organ perfusion. In addition, there are risks of postoperative death and related complications resulting from the surgical intervention itself.

Potential Benefits

The conventional TAR+FET procedure has well-established surgical efficacy. Aortic arch clamping combined with bilateral cerebral perfusion may further reduce circulatory arrest time and overall operative time, decrease in-hospital mortality and related complications, and potentially improve long-term outcomes. Considering the principles of randomized controlled study design, all treatment strategies in this trial aim to maximize the chance of saving patients' lives through surgical intervention.

Quality Control in Clinical Trials

Quality Control Measures

All investigators must adhere to standard operating procedures to ensure the implementation of quality control and quality assurance systems in the clinical trial. All observations and findings in the clinical trial should be verified to ensure data reliability, and all conclusions must be based on original data. Quality control must be implemented at each stage of data processing to ensure that all data are reliable and correctly handled.

Investigator Training

To ensure the quality of the clinical trial, all investigators must undergo training prior to trial initiation. Training includes, but is not limited to, the study protocol, surgical procedures, and the recording and reporting of adverse events. Ongoing training should be provided as needed during the course of the trial. Whenever there

are significant updates to the protocol or relevant documents, retraining of the investigator team is required. Investigators who join the trial after the initial investigator meeting must receive comprehensive training before participating in any trial-related activities.

Enhancing Subject Compliance

Investigators should ensure that informed consent is properly obtained so that subjects fully understand the trial requirements and cooperate with the study.

Investigators should also instruct subjects to promptly report their health status after discharge to monitor the occurrence of adverse events and complications. During follow-up visits, subjects must bring all medications they are currently taking for review of concomitant medications, which should be recorded in the CRF.

Ethical Considerations and Informed Consent in Clinical Trials

Ethical Considerations

Clinical trials must be conducted in accordance with the *Declaration of Helsinki* and relevant national regulations and guidelines for clinical trials.

Prior to the trial, the investigator must submit the study protocol, informed consent form, and other relevant documents to the medical ethics committee of the hospital responsible for the clinical trial. The clinical trial may only commence after approval by the ethics committee. Any amendments to the protocol must also be approved by the ethics committee before implementation. Serious adverse events occurring during the clinical trial must be promptly reported in writing to the ethics committee.

Informed Consent Process

Before enrolling each subject, the investigator is responsible for providing a complete and comprehensive written explanation of the study's purpose, procedures, and potential risks. Subjects must be informed of their right to withdraw from the trial

at any time and assured that their personal information will remain confidential. Each subject must receive a written informed consent form before enrollment, and the investigator must ensure that informed consent is obtained prior to participation. The signed informed consent form should be retained as part of the clinical trial documentation.

If a subject is unable to read, an impartial witness must be present during the informed consent process. After a detailed explanation of the informed consent form, the impartial witness should confirm that the written and oral information are consistent. Upon the subject's oral consent, the impartial witness must sign and date the informed consent form on the same day as the investigator.

Adverse Event Reporting Requirements

Adverse Events

Definition of Adverse Events

An adverse event (AE) refers to any unfavorable medical occurrence that arises during the course of a clinical trial.

Severity of Adverse Events

The severity of adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The grading criteria for adverse events are shown in the table below.

Adverse Event Evaluation Criteria

Severity Grade	Criteria [1]
Grade 1	Mild: asymptomatic or mild symptoms; only clinical or diagnostic observations; no intervention required.
Grade 2	Moderate: minimal, local or noninvasive intervention indicated; Instrumental activities of daily living (IADL) [2] are limited.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; self-care activities of daily living (ADL) [3] are limited.
Grade 4	Life-threatening; urgent intervention indicated.

Grade 5	Death related to adverse event.

Note:

[1] In the criteria, " ; " denotes "or".

[2] Instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing finances, etc.

[3] Self-care activities of daily living include bathing, dressing, eating, using the toilet, taking medications, and remaining in bed as needed.

Management of Adverse Events

General Principles

Once an adverse event occurs, the investigator must ensure that the subject receives adequate and timely treatment and management. All adverse events/serious adverse events must be followed up until one of the following occurs:

① The event resolves.

② The event stabilizes.

③ The event returns to baseline, if a baseline value is acceptable.

④ No further information can be obtained (e.g., the subject or caregiver refuses to provide further information, or the subject is lost to follow-up despite documented efforts).

Special Notes

(1) Vital Sign Changes: During surgery, extracorporeal circulation replaces the subject's own circulatory system, and postoperative recovery of circulatory function takes time. Additionally, postoperative psychological stress, wound pain, and nursing interventions may cause fluctuations in vital signs or require vasoactive or inotropic support. A postoperative mean arterial pressure of 60-90 mmHg is considered reasonable; blood pressure or other vital sign fluctuations outside this range should be assessed by the investigator for clinical significance. If considered potentially life-threatening or requiring urgent intervention, these should be reported as AEs. Non-life-threatening fluctuations or abnormalities in vital signs are not to be recorded as AEs.

(2) Resorptive Fever: Postoperative fever is common due to absorption of sterile

necrotic material. Investigators should evaluate postoperative fever based on symptoms, signs, and laboratory findings. Simple postoperative resorptive fever should not be reported as an AE; if fever is judged to be due to infection or other causes, it should be reported as an AE.

(3) Laboratory Abnormalities: Due to stress response, intraoperative ischemia-reperfusion injury, and anticoagulation during extracorporeal circulation, some laboratory parameters (e.g., blood count, biochemistry, coagulation, blood gases) may be abnormal postoperatively. Investigators should interpret isolated laboratory abnormalities in the context of the subject's symptoms, signs, imaging, and other laboratory findings. Transient, mild abnormalities do not require AE reporting. Progressive or severe abnormalities, or those requiring special intervention, should be reported as AEs.

(4) Anemia: Hemodilution and blood loss during extracorporeal circulation frequently necessitate perioperative transfusion. For perioperative anemia (e.g., decreased hemoglobin or hematocrit), investigators should make a comprehensive assessment based on clinical findings and imaging. Anemia that is corrected by routine transfusion does not require AE reporting; however, ongoing bleeding or transfusion-refractory anemia should be reported as an AE.

(5) Wound Pain: Significant wound pain is common after major cardiac surgery and is generally not reported as an AE. If the pain is persistent, severe, or judged by the investigator to have a serious impact on prognosis, it should be reported as an AE.

(6) Postoperative Fluid Collection: Inflammatory exudate may cause mild postoperative fluid collection at the surgical site, which is usually self-limiting. Investigators should comprehensively assess symptoms, signs, and laboratory data to exclude active bleeding or infection. Fluid collections that are non-progressive and do not require drainage or special intervention are not reported as AEs.

(7) Neuropsychiatric Complications: Postoperative delirium may occur due to reduced cerebral perfusion during extracorporeal circulation and the effects of anesthesia. Psychological stress and wound pain may also result in anxiety,

depression, or sleep disorders. If these symptoms do not require consultation or treatment by a psychiatrist or neurologist, they are not reported as AEs.

Serious Adverse Events

A serious adverse event (SAE) is defined as any event occurring during the clinical trial that results in death or significant deterioration in health, including life-threatening illness or injury, permanent impairment of body structure or function, hospitalization or prolonged hospitalization, or the need for medical intervention to prevent permanent impairment. Events resulting in fetal distress, fetal death, congenital anomaly, or birth defect are also included.

The following hospitalizations are not to be recorded or reported as SAEs: hospitalizations for diagnosis or elective treatment of preexisting conditions, hospitalizations for insurance reimbursement, planned hospitalizations or elective surgeries not related to an adverse event, or admissions for comprehensive physical examination.

Reporting Procedures

If a serious adverse event occurs during a medical device clinical trial, the investigator must immediately take appropriate treatment measures for the subject. At the same time, the investigator must report the serious adverse event to the clinical trial institution management department and the ethics committee within 24 hours of becoming aware of the event. The investigator is also responsible for following up on the serious adverse event according to the clinical trial protocol and submitting a follow-up report regarding the event.

Provisions on Protocol Deviations and Amendments

Protocol Deviations

Clinical trials must adhere to the protocol approved by the ethics committee; any intentional or unintentional conduct that deviates from the protocol is referred to as a

protocol deviation.

According to the responsible party, protocol deviations can be classified into deviations due to non-compliance by the trial institution and deviations caused by subject non-compliance. According to severity, deviations can be categorized as minor or major protocol deviations. Major deviations have one or more of the following attributes: impacting the safety and rights of the subject; affecting the subject's willingness to continue participation; or compromising data quality and integrity. Minor deviations generally do not have these three attributes.

Minor protocol deviations are usually reported periodically to the ethics committee, and investigators must explain the reasons, impact, and measures taken. Major protocol deviations should be reported promptly.

Each protocol deviation should be followed up with corrective or preventive measures to address the error and prevent recurrence of similar deviations.

Measures to Control Protocol Deviations

Sponsor

(1) The protocol should be written in clear language and designed in such a way as to minimize the possibility of protocol deviations; potential deviations should be easy to detect and identify.

(2) During investigator meetings, special training should be provided regarding protocol implementation details and the reporting and monitoring of protocol deviations.

(3) Deviation records should be reviewed periodically to identify trends and systemic errors; corrective actions must be carried out for identified deviations. If immediate protocol or study plan amendments are necessary, the study project should be suspended until correction and retraining are completed.

Investigators

(1) During the project evaluation stage prior to study initiation, investigators

should carefully read the protocol and thoroughly discuss its feasibility at their institution with the sponsor.

(2) During the informed consent process, investigators should explain the importance of protocol adherence to subjects, detail the protocol and trial requirements, and highlight important procedures and follow-up matters.

(3) Investigators must comply with the protocol approved by the ethics committee and must immediately document and explain any deviations if they occur.

Subjects

During the signing of the informed consent form, investigators should explain in detail the requirements of the protocol and highlight important examinations and follow-up matters.

Retraining

Investigators must undergo retraining (and, if necessary, multiple retraining sessions) in the following situations:

(1) Misunderstanding of the protocol occurs;

(2) New investigators join the study;

(3) The research plan is changed;

(4) Reminders are needed regarding protocol details.

Reporting Protocol Deviations

The principal investigator must regularly report the progress of the medical device clinical trial to the ethics committee and promptly report any events affecting participant rights and safety or any protocol deviations.

If, in order to protect the subject’s rights, safety and health, a deviation occurs in an emergency situation and cannot be reported in a timely manner, it must be reported as soon as possible afterwards in writing according to relevant regulations.

If the clinical trial protocol, informed consent, or other files are to be revised, or

if a previously suspended clinical trial is to be resumed, written approval from the ethics committee must be obtained before continuing the trial.

Investigators must strictly adhere to the clinical trial protocol; no deviation or substantive change is permitted without approval from the ethics committee. However, if immediate action is required to eliminate a direct hazard to subjects, a written report should be submitted afterwards.

Protocol Amendments

If, during the trial, investigators believe that the protocol is flawed (e.g., inclusion/exclusion criteria do not cover the target population, difficulty enrolling cases, or sample size does not match clinical reality), the protocol should be amended and submitted to the ethics committee for approval.

Progress Schedule

Key Task	Timeline
Clinical Trial Initiation Meeting	May 2025 - June 2025
Ethics Committee Approval	May 2025-June 2025
First Subject Enrollment	June 2025
Last Subject Enrollment	May 2026
Completion of Follow-up for All Subjects	May 2027
Database Lock	May 2027
Completion of Final Report	June 2027

Follow-up and Medical Measures After Completion of the Trial

After the end of the trial, subjects will no longer be followed up. Subsequent medical measures will be determined jointly by the investigator and the subject, based on actual clinical management of the disease.

Responsibilities of Each Party

(1) Medical and Health Institutions: Bear primary responsibility for clinical research implementation, establish and improve the organizational, quality assurance, conflict-of-interest prevention, and subject right-protection systems for scientific,

standardized, and orderly clinical research, and ensure quality assurance and full-process management for clinical research.

(2) Institutional Office: Responsible for project review, process management, quality management, contract management, close-out, and file management of clinical research, and coordinate scientific and ethical reviews.

(3) Academic Committee: Comprised of relevant institutional leaders, functional department heads, and clinical research experts, responsible for scientific review of clinical research, including rationality, necessity, feasibility, research objectives, intervention measures, study hypotheses, methods, sample size, endpoints, and safety.

(4) Ethics Committee: Protects the rights and safety of subjects, with special attention to vulnerable populations. Reviews the scientific and ethical aspects of clinical trials throughout the entire process.

(5) Principal Investigator: The project leader participating in the clinical trial; responsible for drafting the protocol, initiating and managing the trial, and ensuring the scientific validity and ethical compliance of the study.

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