Multicenter Comparative Study on the Diagnostic Efficacy of "Ultra-high Sensitivity" Cardiomagnetic Detection and Myocardial Nucleoradiology Scanning for Early Diagnosis of Myocardial Ischemia

Study Protocol

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Research Team:Chongqing Emergency Medical Center

Hangzhou Institute of Extermely-weak Magnetic Field Major National Science and Technology Infras tructure

Qilu Hospital of Shandong University

Directory

1.Background information

1.1 Disease background and epidemiology

Coronary atherosclerotic heart disease (CHD) is characterized by its high incidence and severe impact. With the acceleration of the aging process, the incidence and mortality of CHD in China are continuously increasing, making it one of the major chronic diseases affecting the health of the Chinese people. In recent years, with the rapid development of evidence-based medicine and interventional cardiology, the clinical significance of coronary microvascular disease (CMVD) has increasingly gained attention. Previous clinical studies have shown that in patients with myocardial ischemic symptoms but with non-obstructive lesions on coronary angiography, the incidence of CMVD is approximately 45% to 60%[1]. In 2020, the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and the ESC jointly released a consensus document on ischemia with non-obstructive coronary artery (INOCA), proposing that CMVD and/or epicardial coronary vasospasm are the main causes of INOCA.

Whether CHD patients choose conservative drug therapy or interventional treatment after coronary angiography, or the treatment plan for CMVD patients, all are closely related to whether there is myocardial ischemia. Furthermore, the degree of myocardial ischemia varies significantly among individual patients, leading to different clinical treatment decisions. The current established method for detecting myocardial ischemia is emission computed tomography (ECT), which utilizes a radiotracer labeled with thallium-201 or technetium-99m. By recording the radioactivity in the myocardium during rest or stress conditions, it can identify segmental decreases in myocardial perfusion, perfusion defects, or redistribution phenomena in both states, thereby diagnosing myocardial ischemia. The advantage of this technology is its high diagnostic sensitivity and negative predictive value, but its disadvantages include low spatial resolution and radiation exposure. The latter especially makes it difficult for patients to undergo timely examinations, resulting in delays in the early diagnosis of myocardial ischemia. In contrast, ultra-high sensitivity magnetic detection can non-invasively and without contact or radiation damage early and rapidly detect the extremely weak magnetic fields of the heart, which is expected to achieve precise early identification of myocardial ischemia, thus guiding patient treatment.

1.2 Research and development background

Magnetocardiography (MCG) is a non-invasive, risk-free, and contactless technology that characterizes the local magnetic field signals generated by the electrical activity of the heart[2]. The magnetic signals from the heart and the electrical signals from the heart are of the same origin. The ionic activity within myocardial cells forms volume currents, and the curve representing the potential difference caused by these currents on the body surface over time is known as the Electrocardiogram (ECG)[3]. The spatial magnetic field changes caused by volume currents are referred to as magnetocardiograms[4]. Magnetocardiograms are constructed by recording the magnetic signals of the heart using a multi-channel sensor array placed above the chest, thereby mapping the heart's magnetic field. By analyzing these magnetic maps, abnormal electrical activities of the heart can be detected, including myocardial ischemia, arrhythmias, and myocardial diseases[5]. Traditional ECG detection technology is affected by various conductivities of human tissues and skin[6], whereas the magnetic signals used in magnetocardiograms can pass through the body with almost no interference. Therefore, magnetocardiography theoretically offers more

clinically useful information, with the advantages of being non-invasive, safe, and fast, enabling earlier and more accurate diagnoses of potential heart diseases[7,8].

With the development of biomagnetic detection technology and the updating of detection equipment, the new generation of Spin-exchange relaxation-free (SERF) atomic magnetometers achieves a high density of alkali metal vapor by high temperatures, suppresses spin-exchange relaxation, and realizes a very high low-frequency magnetic field sensitivity in weak magnetic fields. Recently, our country has successfully developed a heart magnetic measurement device based on spin-exchange relaxation-free magnetic measurement technology. This device has successfully completed 64-channel time-sharing heart magnetometry and 32-channel synchronous heart magnetometry. It can dynamically display the changes in heart magnetic topography and current density maps, reflecting the corresponding electrophysiological activities of the heart. The device has the capability to perform heart magnetometry in a free environment for the human body, making clinical research on "ultra-high sensitivity"magnetocardiogram possible.

MCG imaging equipment represents a high-end medical device in the quantum precision measurement era. Utilizing ultra-weak magnetic field detection and high-performance magnetic shielding technologies, it captures subtle changes in cardiac magnetic signals reflecting human heart function. This technology offers a novel approach for the clinical diagnosis and assessment of cardiovascular diseases, demonstrating promising applications across the medical field.This study is based on a "ultra-high sensitivity" cardiomagnetic detection device that captures spatial magnetic field changes in ischemic myocardial cells, providing early warning, early diagnosis, and localization detection for myocardial ischemia, thereby serving public health（Figure 1）.

Figure 1 Domestic "ultra-high sensitivity" cardiomagnetic detection device

1.3 Basic product information

The device consists of an array of magnetometer sensors, a high-performance magnetic shielding system, a multifunctional bed, and a heart magnetic signal processing system. Featuring exceptional sensitivity for ultra-weak

magnetic signal detection, it enables high-resolution monitoring of faint magnetic fields generated by the human cardio-electrophysiological network. With advantages including contact-free operation, high precision, and rapid testing capabilities, this system represents a truly functional diagnostic tool for cardiac assessment.

MCG signals and ECG signals share the same origin. The ionic activities in myocardial cells generate volume currents. The curve of potential difference on the body surface changing with time caused by these currents is called an ECG, while the spatial magnetic field changes formed by the volume currents are referred to as a MCG[1]. MCG devices are non-invasive and contactless systems designed to map the localized magnetic field signals generated by cardiac electrical activity[2]. MCG systems construct magnetic field maps of the heart by recording cardiac magnetic signals using multi-channel sensor arrays positioned above the chest [3]. Analysis of these MCG maps enables the identification of abnormal cardiac electrical activities[4]. Traditionally, ECGs are affected by the conductivity of human tissues and skin. In contrast, compared to electrocardiograms, cardiac magnetic signals can pass through the human body almost undisturbed, providing more clinically useful functional information, thereby allowing for a more advanced and accurate assessment of myocardial electrophysiological conditions[5, 6].

The core component of the heart magnetic detection device is the SERF atomic magnetometer, which uses a novel alkali metal atom operating in the SERF state to achieve extremely weak magnetic measurements. It has advantages such as non-cryogenic operation (traditional magnetometers require cooling with liquid helium), miniaturization, and high spatial resolution.The basic principle is: using high temperature to achieve a higher density of alkali metal vapor in the gas cell, suppressing spin-exchange relaxation, and using polarized detection light that is perpendicular to the pump light entering the gas cell to measure the Larmor precession frequency of spin-polarized atoms in a weak magnetic field, thus accurately reflecting the magnitude of the external magnetic field. The SERF magnetometer has achieved high sensitivity to low-frequency magnetic fields in weak magnetic fields. The magnetic field of the heart is only 10^{-7} times the intensity of the Earth's magnetic field signal, and the new generation of SERF atomic magnetometers makes the study of "ultra-high sensitivity" cardiac magnetometry possible.

1.4 Scope of application and related information

Product Name: "Ultra-high Sensitivity" Cardiomagnetic Detection Device

Product Performance Structure and Composition: The heart magnetic detection device consists of a magnetic shielding system, a magnetic field detection array, a movable examination bed, heart magnetic imaging software, and a main control system.

Expected Use: To collect and record the magnetic signals of the human heart.

Target Population: Individuals requiring examination for heart diseases or health check-ups.

International studies on SQUID (Superconducting Quantum Interference Device)-based magnetocardiography have preliminarily demonstrated MCG's diagnostic efficacy for conditions like myocardial ischemia [9-11]. However, its clinical adoption faces significant constraints due to complex operational requirements (e.g., cryogenic environments), high costs, intricate diagnostic modeling parameters, lack of standardized protocols, and limited patient cohort sizes[1]. With the advent of domestically developed high-performance SERF-MCG systems, there is an urgent need to conduct large-scale clinical validation studies assessing MCG's capability for myocardial ischemia

detection. Such research is crucial for advancing China's premium medical equipment toward domestic and global market penetration.

2.Research purposes

Primary Objective: To compare the consistency of "ultra-high sensitivity" cardiomagnetic detection with resting and stress ECT (exercise stress and pharmacological stress) in diagnosing myocardial ischemia.

Secondary objective: To study the diagnostic efficacy (specificity and sensitivity) of "ultra-high sensitivity" cardiomagnetic detection of myocardial ischemia using ECT as a reference, and to explore the value of domestically produced "ultra-high sensitivity" cardiac magnet detection for myocardial ischemia.

3. Study design

3.1 General Design

This study is a prospective, multi-center comparative study. Patients with symptoms of myocardial ischemia who are considered for the diagnosis of CHD or CMVD and are scheduled for ECT examination will be included. Subjects will be randomly recruited, and a domestically manufactured "ultra-high sensitivity" cardiomagnetic detection device will be used to collect cardiac magnetic images. The ECT examination will be completed within one week. A consistency analysis will be conducted between the cardiac magnetic results and the ECT results to evaluate the early diagnostic efficacy of cardiac magnetic detection for myocardial ischemia. Subgroup analyses will also be performed based on resting and stress conditions.

3.2 Subject selection

Inclusion Criteria

1）Age ≥18 years;

2）Presence of myocardial ischemia-related symptoms (e.g., angina pectoris) with suspected CHD or CMVD, scheduled for ECT examination;

3）Signed informed consent form.

Exclusion Criteria

1）Hemodynamic instability (systolic blood pressure <90 mmHg or requiring vasoactive drugs);

2）Cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, severe sinus bradycardia and sinus pauses, and second - degree or higher - degree atrioventricular block and other severe arrhythmias;

3）Aortic dissection aneurysm, severe aortic valve stenosis or insufficiency;

4）Elderly or frail patients with neuromuscular or osteoarticular diseases who cannot complete exercise stress ECT;

5）Allergy to drugs used in pharmacologic stress ECT;

6）Patients with severe renal insufficiency with an estimated glomerular filtration rate (eGFR) < 30 ml/min or those undergoing dialysis;

7）Patients with malignant tumors and a life - expectancy of less than1 year;

8）Pregnant or lactating women;

9）Patients unable to undergo MCG examination due to inability to enter the chamber, metallic implant interference, or other conditions deemed unsuitable by researchers.

3.3 evaluation method

3.3.1.Primary Evaluation Indicators

Evaluation Indicators: Diagnostic concordance between " ultra-high sensitivity" magnetocardiography (MCG) and rest/stress ECT (including exercise and pharmacological stress protocols) for detecting myocardial ischemia.

Criteria and Measurement Methods: Paired comparative design where all subjects undergo both ECT and MCG examinations, with consistency analysis of diagnostic outcomes between modalities.

3.3.2 Secondary Evaluation Indicators

Evaluation Indicators:Using ECT as a control, to study the diagnostic efficacy (specificity and sensitivity) of "ultra-high sensitivity" cardiomagnetic detection for myocardial ischemia, and to explore the value of domestic "ultra-high sensitivity" cardiomagnetic detection for myocardial ischemia.

Criteria and Measurement Methods: Myocardial ischemia is defined according to the results of ECT detection. Based on the degree of myocardial perfusion defects, patients are categorized into no myocardial ischemia, mild myocardial ischemia, moderate myocardial ischemia, and severe myocardial ischemia, with the ischemic area calculated. The performance evaluation differentiation indicators include sensitivity, specificity, area under the receiver operating characteristic curve (Area under ROC curve, AUC), recall rate, and F1 score, among others.

3.4 Bias control measures

This study may have selection bias, information bias, and confounding bias.

Selection bias may specifically manifest as enrollment population bias, such as too few ECT-negative individuals for myocardial ischemia or a higher mean age in the study cohort. The control measure is to strictly adhere to inclusion and exclusion criteria to ensure the representativeness of the study population.

Information bias may arise from misunderstandings of variables, leading to biased values. For example, there can be significant differences in responses when individuals have varying understandings of the same variable. The control measure is to establish a unified and standardized definition for the variables. Additionally, the scientific attitude of the participants is crucial. Through standardized training and strict requirements, we can minimize such biases as much as possible. Anomalies in cardiac magnetic signals can cause parameter deviations, leading to information bias, such as single-channel abnormalities, external magnetic wave interference, and metal interference (Figure 2). Control measures include selecting a room with minimal external interference when locating the cardiac magnetic room, confirming the absence of external interference before conducting a cardiac magnetic examination, checking if the patient has any metal on them, and ensuring that individual probes are not damaged. Personnel involved in the cardiac magnetic signal collection should strictly adhere to collection protocols and carry out regular maintenance of the equipment.

Confounding bias may arise from risk factors such as diabetes mellitus and hypertension, as well as electrophysiological alterations induced by anxiety, depression, or emotional stress, causing interference with MCG-

based myocardial ischemia detection. Quality control will be implemented during statistical analysis through matching, pseudo-randomization, and stratified analysis based on specific circumstances.

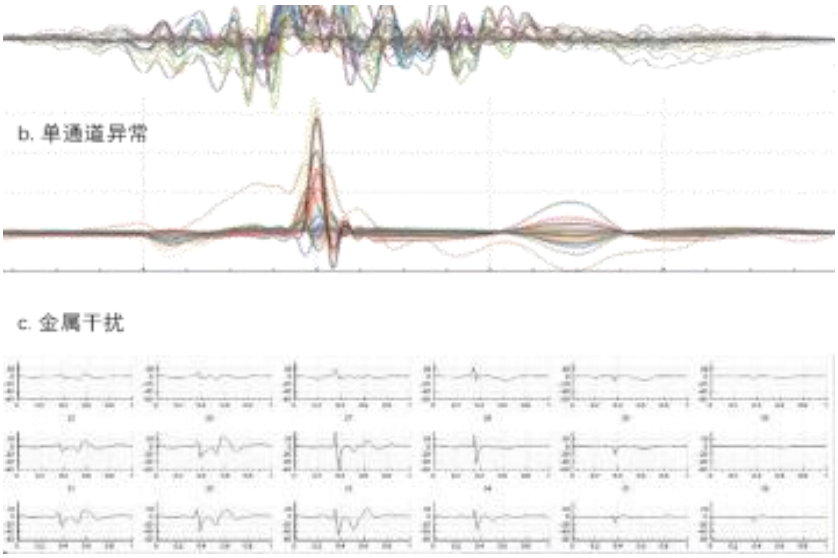

Figure 2 Preventing information bias caused by interference or abnormality of magnetocardiographic signals

4. Statistical Analysis

4.1 Sample size estimation

In this project sample size calculation was performed to ensure the statistical reliability of the study. By considering factors such as the expected effect size and significance level, an appropriate sample size was determined. This ensures sufficient support for testing the study hypothesis, guarantees scientifically credible results, enhances study reproducibility, and boosts data analysis robustness, thereby making the study conclusions more convincing and reliable.

For testing the non - inferiority of cardiomagnetic evaluation of myocardial ischemia compared to ECT, the sample size estimation used the method for comparing paired two - sample rates in a non - inferiority design and was calculated as follows:

$$n=(Z_{\alpha}+Z_{\beta})^2\times(p_1(1-p_1)+p2(1-p_2))/(p_1-p_2-\Delta)^2$$

In the formula：

Z_{α} is the critical value of the standard normal distribution;

Z_{β} is the critical value of the standard normal distribution corresponding to the power;

P_1 and P_2 represent the positive rates of the control group and the intervention group, respectively;

Δ: non-inferiority margin;

α: significance level;

β: power of the test.

The preliminary experimental results indicated a 77% positive rate for cardiomagnetic detection and 71% for ECT， with α=0.05 (one - sided), β=0.2 (power 80%), and Δ=0.05. We calculated the minimum sample size to be 196 cases, with a total sample size of 196 cases. Considering a dropout rate of 10%, the final determined sample size was 218 cases.

4.2 Statistical methods

Unless otherwise stated, the following general principles will be used for statistical analysis of the study data.

For categorical variables, statistical descriptions will be provided as the number and percentage of participants in each category. For continuous variables, the mean, standard deviation, median, Q1， Q3 and extremes will be listed. Diagnostic efficiency will be evaluated using sensitivity, specificity, AUC, recall, and F1 score for discrimination. Calibration will be assessed via calibration curves and the Hosmer-Lemeshow (H-L) test. Subgroup analyses will be conducted for rest ECT and stress ECT groups to compare diagnostic efficiency and consistency. The Pearson correlation coefficient will assess the linear relationship between cardiomagnetic scores and ECT ischemic areas, with the correlation coefficient (r) and significance level (p value) reported. The Kappa coefficient will evaluate the consistency of cardiomagnetic detection with rest and stress ECT in diagnosing myocardial ischemia, with the consistency level reported.All statistical tests will use a significance level of 0.05.

5.study flow

The study is aimed at selecting and enrolling patients who come to the hospital with symptoms of myocardial ischemia such as chest tightness and chest pain, suspected of having CHD or CMVD, and who are scheduled to undergo ECT. For patients who have already undergone coronary CTA or CAG and are scheduled for ECT, after an initial screening, a consent form will be signed, and inclusion/exclusion criteria will be re-verified. Patients successfully enrolled will undergo cardiomagnetic detection. For patients with acute myocardial infarction, cardiomagnetic detection will be performed once the condition allows and ECT will be completed within one week. Outpatients and inpatients, except those with contraindications for burden ECT, are required to undergo both resting and burden ECT. After completing the relevant examinations (Table 1, research flow chart), data required for the study will be collected according to the Case Report Form (CRF) requirements.

project	screening	Before magnetocardiography	Magnetocardiographic testing	In-hospital inspection and observation
signed the informed consent form[1]	√			
demographic data	√			

Medical history, current medical history[2]	√			
Height, weight		√		
Blood pressure[3]		√		
ECG[4]		√		
Coronary CTA or angiography[5]				√
Magnetocardiography			√	
Echocardiography[6]				√
ECT[7]				√

Table 1 research flow chart

[1] Written informed consent must be obtained from the subject or guardian before screening can begin。
[2] The current medical history needs to record the characteristics and duration of chest pain symptoms。
[3] Blood pressure was measured before magnetic examination to assess patient condition。
[4] ECG examination was performed within 5min before/after MCT examination, and ECG data were exported as original electronic data。
[5] According to routine clinical diagnosis and treatment examinations, DICOM format is regularly exported and submitted to the center for QFR/CTFFR calibration.。
[6] According to routine clinical diagnosis and treatment examinations, the study only records test results。
[7] The patient underwent cardiac magnetic examination within one week after the ECT scan。

ECT Imaging Protocol:

(1) Patient Preparation before Imaging:

① It is advisable to be fasting. Patients undergoing a load test in the late morning or afternoon may consume a light diet; it is recommended that insulin-dependent diabetic patients schedule the load test in the morning.

② Discontinue the consumption of caffeine-containing beverages, tea, food, and medications for 24 hours before the load test; discontinue the use of methylxanthine medications for 36 hours.

③ Discontinue short-acting nitrates at least 2 hours before the load test and long-acting nitrates for at least 6 hours.

④ Discontinue calcium channel blockers within 24 hours before the load test, and β-blockers within 48 hours.

（2）Imaging Method

Key Points of Imaging Technology (taking the two-day or one-day gated stress/rest imaging method using 99mTc-labeled imaging agents as an example):

1. Imaging Agent: ^{99m}Tc-Methoxyisobutylnitrile (MIBI) or ^{99m}Tc-Tetrofosmin (TC).

2. Imaging Methods:

^{99m}Tc-MIBI Stress-Rest Two-Day Imaging Method: Inject intravenously 740-925 MBq (20-25 mCi) at peak stress, perform imaging 1.0-1.5 hours later, then inject 740-925 MBq (20-25 mCi) the next day and perform imaging again 1.0-1.5 hours later.

^{99m}Tc-MIBI Exercise-Rest One-Day Imaging Method: Inject 296-222 MBq (8-9 mCi) at rest, perform rest imaging 1.0-1.5 hours later, then perform exercise testing 1-4 hours later and reinject 814-925 MBq (22-25 mCi) followed by imaging 1.0-1.5 hours later.

3. Precautions: After intravenous injection of the imaging agent, have a fatty meal 30 minutes later to reduce interference from radioactive drugs in the liver and gallbladder on the images of the left ventricle's inferior wall.

4. Imaging Sequence: For the two-day method, rest imaging can be done before stress imaging or vice versa; for the one-day method, it is recommended to perform rest imaging before stress imaging.

5. Stress Test: Commonly employs exercise stress (treadmill or bicycle) or pharmacological stress (Regadenoson, Adenosine, ATP, or Dipyridamole). Detailed recommendations for the stress test should be provided, including testing environment, related equipment, stress protocols, emergency equipment, drug preparation, and emergency plans. Physicians responsible for the stress test should have received formal training in patient rescue or be assisted by a cardiologist to monitor the subjects. If the patient can exercise and is expected to reach the stress level, exercise testing is preferred; otherwise, pharmacological stress testing should be performed. For patients with left bundle branch block, pre-excitation syndrome, or those who have undergone pacemaker implantation, pharmacological stress testing should be the first choice. The basic principle is to meet the indicators of the stress test as much as possible, complete the comparison analysis of the stress and rest gated MPI, and pay attention to analyze positive indicator information provided by the stress test and its monitored ECG (such as ST segment changes, arrhythmias, angina attacks, etc.).

6.clinical monitoring

To safeguard participants' rights and ensure the trial data is accurate, complete, and reliable and that the implementation is in line with the study protocol, the center appoints monitors to visit the research unit regularly or as per actual needs to carry out monitoring work.

Monitors' responsibilities include: （1）Pre - trial checks to confirm the trial - undertaking unit has proper conditions, such as adequate and well - trained staff, well - functioning equipment, necessary examination facilities, sufficient participants, and researchers familiar with the protocol.

（2）During the trial, monitoring researchers' protocol compliance, confirming informed consent from all participants, and ensuring eligible participants are enrolled.

（3）Verifying the accuracy and completeness of data records and reports, and ensuring correct data entry in case report forms that matches source data.

7. Data management

Before the first participant is enrolled, the data manager sets up eCRFs (Electronic case report form) and logic verification procedures in the EDC (Electronic data capture system) system as per the protocol, completes user

testing, and launches it. All EDC users must finish relevant training, have records filed, and then can access the study's eCRF. When using electronic signatures on eCRFs, users need to confirm and agree to the relevant statement. Accounts are for individual use only, and passwords should be well - kept and changed regularly. If there are personnel changes in the study team, access rights need to be revoked timely.

The EDC system's verification logic procedure checks the completeness and logic of entered data, and flags potential issues. Investigators or data entry personnel can correct data or respond to queries for clarification and confirmation. Monitors, quality control personnel, and data managers review eCRF data and may query questionable data. Investigators should promptly respond to system - generated and personnel - issued queries, which may be repeated until data issues are resolved. Before database lock, the study team must complete data cleaning and hold a data review meeting to finalize the analysis population, with all decisions documented. After the meeting, the team confirms the EDC database lock, making data unchangeable. Upon study completion, the EDC system generates PDF eCRFs, saved on read - only discs by the center. Study materials are preserved and managed per GCP, with essential documents kept for at least 10 years post - study.

8.Risk benefit analysis

The safety risks of the interventions in this study are low. Electrocardiograms (ECG), coronary angiography (CAG), coronary CT angiography (CTA), and SPECT have been used clinically for many years, ensuring their safety. The magnetic cardiogram examination is conducted in a weak magnetic field environment, is non-invasive, and involves no radiation, which almost eliminates any additional risk. During the execution of the study, researchers must provide clear explanations about informed consent and also adequately disclose the risks associated with this study. Patients scheduled for CAG/CTA or SPECT may experience anxiety, and researchers should possess ample clinical and research experience to ensure normal patient care and handle any emergencies effectively, thereby ensuring the smooth implementation of the project.

9.Quality assurance and quality control

To ensure trial quality, before the official start of the study, the central unit and researchers should discuss and formulate the clinical research plan together. It should be confirmed whether the relevant researchers participating in the trial have received appropriate GCP training. According to GCP guidelines, necessary steps should be taken during the design and implementation phases of the study to ensure that the data collected is accurate, consistent, complete, and credible. All data in clinical trials should be verified and recorded in a timely manner to ensure data reliability. The instruments and equipment used for various inspection items in clinical trials should meet strict quality standards and ensure they are functioning properly. Researchers will input the information required by the protocol into the eCRF, which will be verified by monitors for completeness and accuracy, and necessary corrections and explanations will be made by the researchers based on actual circumstances. The research center will establish quality management personnel to conduct necessary supervision of clinical trials. Monitors will systematically check clinical research-related activities and documents to evaluate whether they are conducted in accordance with the study protocol, investigator's brochure, and relevant regulations, and whether research data is recorded in a timely, truthful, accurate, and complete manner.

10.principle of confidentiality

The confidentiality of subject information will be strictly enforced by the researchers and participating research personnel. The research protocol, documents, data, and all other information generated will be kept strictly confidential. No relevant research or data information shall be disclosed to any unauthorized third party without the prior written approval of the central unit. Authorized representatives of the central unit, ethics committees, and regulatory authorities can inspect all documents and records that the researchers are required to maintain, including but not limited to: medical records and subject records, and the research center shall allow access to these records. The contact information of the subjects will be securely stored and used only internally during the research process. At the end of the research, all records will continue to be stored securely for the duration specified by the local ethics committee and regulations. The subject research data collected for statistical analysis and scientific reporting will be uploaded and stored at the research center. The research data entry and research management systems used by researchers at each clinical research center are confidential and password protected. At the end of the research, all identifying information in the research database will be eliminated and archived at the research center.

The information contained in this research protocol is only provided to the project's researchers, the clinical research management committee, and relevant institutions for review. Without the approval of the principal investigator, it is strictly forbidden to disclose any information to third parties that are not related to this research.

11.Time plan

2025.06—2025.10 Research training and preparation, with sub-centers kicking off one by one.

2025.10—2026.10 Complete recruitment and preliminary data entry, quality control, and verification, and conduct an initial analysis and evaluation.

2026.10—2026.12 Complete data tracing, cleaning, and database lock, analyze final results, and generate the report.

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