Pressure Guidewire System Multi-center,

Prospective, Single-subject Design Clinical Trial

Updated document date: July 11, 2022

Protocol No.:WXYL-LC-2018001

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Prospective, Single-subject Design Clinical Trial

Name of investigational medical device: Zurich Pressure Guidewire System Model100

Management category of investigational medical device:

Class III medical devices requiring review and approval through clinical trial Yes☐ No■

Predicate products within the territory of China Yes■ No☐

Clinical protocol version number: v1.0

Document date: July 11th, 2018

Investigational Site: Fudan University Zhongshan Hospital

Principle Investigator: Dr. Ge Junbo

Sponsor: Zurich Medical Inc.

Agent: Shandong Visee Medical Devices Co., Ltd.

Contract Research Organization (CRO): Beijing Jingruitianhe Medical Science and Technology Development Co., Ltd.

Instructions for filling:

1. For multi-center clinical trials, only the principal investigational site shall be listed on the cover, while other sites shall be listed in the contents of the protocol.

2. For multi-center clinical trials, the coordinating investigator shall be filled out as the investigator on the cover.

Contents

Abbreviations table

Abbreviations	Full name in English
AE	Adverse Event
ALT	Alanine Transaminase
AO	Aortic output
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AUC	Area Under Curve
BUN	Blood Urea Nitrogen
CAD	Coronary Artery Disease
CFDA	China Food and Drug Administration
CK	Creatine Kinase
CK-MB	Createine Kinase-MB
CR	Creatinine
EC	Ethics Committee
EDC	Electronic Data Capture
FAS	Full Analysis Set
FFR	Fractional Flow Reserve
FFR_{PW}	Fractional Flow Reserve Pressure Wire
FFR_{WS}	Fractional Flow Reserve Wire System
FPR	False Positive Rate
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICA	Invasive Coronary Angiography

Abbreviations	Full name in English
in.	inch
ITD	Intention To Diagnostic
kg	kilogram
min	minute
mm	millimeter
mmHg	millimeter(s) of mercury
NPV	Negative Predictive Value
NYHA	New York Heart Association
Pa	Arterial Pressure
Pd	Distal Coronary
PPV	Positive Predictive Value
PLT	Platelets
ROC	Receiver Operating Characteristic
PPS	Per Protocol Set
RBC	Red Blood Count
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SOP	Standard Operating Procedure
SS	Safety Set
cTNI	cTroponin I
cTNT	cTroponin T
TPR	True Positive Rate

Abbreviations	Full name in English
ug	Microgram
WBC	White Blood Count

Protocol Summary

Protocol Name	Pressure guidewire system multi-center, prospective, single-subject design clinical trial
Objective	To Evaluate the effectiveness and safety of Zurich Medical's pressure guidewire system (including guidewire with high-fidelity sensors and a unique paired portable display unit), which is used to measure the coronary artery blood fractional flow reserve (FFR) to diagnose coronary artery disease, and to direct a catheter through a blood vessel.
Study Device Names	Investigational device: pressure guidewire system (including wire with high-fidelity sensor strains and unique paired portable display units) Model:100 Sponsor: Zurich Medical Inc. Agent: Shandong Visee Medical Devices Co., Ltd. Control group device: pressure guidewire Model: C12008 Manufacturer: St. Jude Medical, China Agent: St. Jude Medical (Shanghai) Co., Ltd. Registration license number: 国械注进20143775272 Analyzer Express Model:12711 Manufacturer: St. Jude Medical, China Agent: St. Jude Medical (Shanghai) Co., Ltd. Registration license number: 国食药监械（进）字2013第3211615
Indication For Use	For patients who need coronary angiographic examination and coronary interventional treatment, pressure guidewire system is indicated to calculate the patient's blood fractional flow reserve (FFR), and to assist the physicians to make clinical decisions.

Trial Design	This clinical trial uses a multi-center, prospective, single-subject design trial method, using St. Jude Medical's pressure guidewire and Analyzer Express as a control device. The subjects who met the criteria for this study will be registered with the central registration system after enrollment. The subject's fractional flow reserve of coronary artery stenosis will first be measured using investigational device and recorded, and then measured using control device and recorded. The safety follow-up period is 48 hours.
Number of centers	Trial is expected to be held simultaneously at 5 centers in mainland China.
Sample size	300
Trial duration	The overall duration of clinical trials includes the time of signing of clinical trial site's agreements with all participating hospitals, the time of review and approval of the ethnic committee meeting and the post-meeting opinion rectification, filing time, the trial kickoff, the enrollment and the subject's FFR measurement, the data collection, statistics, summary report writing time, etc., and is expected to be 2 years.
Inclusion Criteria	1） Age 18 to 75 years old, gender-unrestricted, non-pregnant female; 2） Understand and be willing to sign an informed consent form; 3） Diagnosed with coronary heart disease; 4） Intrusive ICA and FFR measurement are needed; 5） Visual coronary angiography showed at least one moderate stenosis lesion (diameter stenosis of 30% - 70%) on the coronary artery with diameter ≥ 2.5mm
Exclusion Criteria	1） Patient who do not understand or are unwilling to sign an informed consent form; 2） Has a history of myocardial infarction; 3） Patient with other serious diseases are not suitable for clinical trials, such as a complex congenital heart disease history,

	severe heart failure(NYHA cardiac function level IV), long QT syndrome, severe hypertension, Severe asthma, severe chronic obstructive pulmonary disease, liver and kidney dysfunction and other serious infections and critical illnesses; 4） Coronary intervention surgery contraindications; 5） Patient with ATP contraindications (ATP contraindications: sinus syndrome, sinus insufficiency and the elderly with cautious use or no use); 6） The clinical manifestations of patients show acute instability, including acute chest pain (sudden appearance), cardiogenic shock, unstable blood pressure (systolic pressure less than 90mmHg), severe congestive heart failure or acute pulmonary edema; 7） The angiography shown or suspect of thrombosis; 8） The angiography shown or suspect of dissection; 9） Left main coronary artery disease, target blood vessels with severe curvature or calcification lesions, total occlusion; 10）There are any other factors that the investigator considers unsuitable for inclusion or completion of this study.
Primary Effectiveness Endpoint	Diagnostic consistency rate: When the measurement of control device is positive ($FFR_{PW} \leq 0.80$) or negative ($FFR_{PW} > 0.80$), investigational device is also positive ($FFR_{WS} \leq 0.80$) or negative ($FFR_{WS} > 0.80$). Each subject will be considered a research unit (for patients with multiple lesions, the method of converting the results of multiple lesions into patient level is defined in the statistical analysis plan), and the coronary artery FFR_{PW} measured by control device will be taken as reference.
Secondary Effectiv	1) The sensitivity and specificity of the investigational device used to diagnose coronary heart disease: Taking the subject as the research unit, the sensitivity and specificity of

eness Endpoint	investigational device for diagnosis of coronary heart disease will be calculated. FFR_{PW} of coronary artery measured by control device will be used as the reference and $FFR_{PW} \leq 0.80$ as positive threshold 2) Positive predictive value, negative predictive value and area under working characteristic curve: Taking subjects as research units, FFR_{PW} measured by Control Device as reference, and $FFR_{PW} < 0.80$ as positive threshold, the positive predictive value, negative predictive value and area under ROC curve (AUC) of investigational device for diagnosis of coronary heart disease will be calculated. 3) Passing-Bablok Regression Analysis: Taking the blood vessel as the research unit, Passing-Bablok regression analysis will be used to analyze the FFR_{WS} value of coronary artery measured by the investigational device and the FFR_{PW} value of coronary artery measured by the control device. 4) Bland-Altman Deviation Analysis: Taking the blood vessel as the research unit, Bland-Altman deviation analysis will be used to analyze the FFR_{WS} value of coronary artery measured by the investigational device and the FFR_{PW} value of coronary artery measured by the control device. 5) Pearson linear correlation analysis: Taking the blood vessel as the research unit, Pearson linear correlation analysis will be used to analyze the FFR_{WS} value of coronary artery measured by the investigational device and the FFR_{PW} value of coronary artery measured by the control device. 6) Device success rate: Taking the blood vessel as the research unit, Effective FFR_{WS} and FFR_{PW} readings will be used as the criteria to judge the success rate of the devices, and the success rate of the investigational device and the control device will be compared.
Safety	The occurrence of adverse events and device defects will be

Endpoint	used as a safety evaluation index.

1 SPONSOR INFORMATION

1.1 Name Of The Sponsor

Zurich Medical Inc.

1.2 The Address Of The Sponsor

2405 Xenium Lane N, Plymouth, MN 55441 USA

1.3 Sponsor's Contact Information

Phone:001-651-571-0020 Email:info@zurichmed.com

1.4 Agent's Name, Address, Contact Details and Related Qualification Documents

Agent Name: Shandong Visee Medical Devices Co., Ltd.

Address: 10 Junshan Road, Chucun Town, Torch High-Tech Industrial Development Zone in Weihai City, Shandong Province

Contact: Tel: 0631-5716452 Fax: 0631-5621156

2 LIST OF ALL INVESTIGATIONAL SITES AND INVESTIGATORS FOR MULTI-CENTER CLINICAL TRIALS:

Investigational Site Code	Name of investigational site	Investigators
01	Fudan University Zhongshan Hospital	Ge Junbo
02	The First Hospital of Lanzhou University	Zhang Zheng
03	The First Affiliated Hospital of XiAn Jiaotong University	Yuan Zuyi
04	The People's Hospital of Liaoning Province	Li Zhanquan

05	Remin Hospital of Wuhan University People's Hospital	Jiang Xuejun

3 OBJECTIVE AND CONTENT OF CLINICAL TRIAL

3.1 Objective

To Evaluate the effectiveness and safety of Zurich Medical's pressure guidewire system (including guidewire with high-fidelity sensors and a unique paired portable display unit), which is used to measure the coronary artery blood fractional flow reserve (FFR) to diagnose coronary heart disease, and to direct a catheter through a blood vessel. Including:

Effectiveness: Coronary artery Fractional Flow Reserve(FFR) measured by control device, St. Jude Medical's Pressure Guidewire and Analyzer Express (FFR_{PW}) will be used as a reference to evaluate FFR measured by Investigational device, the Zurich Medical pressure guidewire system (including wire with high-fidelity sensor strains and unique paired portable display units) (FFRws)'s efficacy to diagnose coronary artery disease via diagnostic consistency, sensitivity, specificity, positive predictive value, negative predictive value, and Area Under the Curve (AUC) of Receiver Operating Characteristic (ROC). Meanwhile, Passing-Bablok regression analysis, Bland-Altman deviation analysis and Pearson correlation analysis of the FFRpw and FFRws will be used to evaluate the success rate of the investigational device.

Safety: The adverse events and device defects that occur during Zurich Medical's pressure guidewire system measurement of coronary arterial FFRws will be mainly evaluated.

3.2 Content

This clinical trial is designed as a multi-center, prospective, single-subject design trial. The investigational device is Zurich Medical Pressure Guidewire System (including wire with high-fidelity sensor strains and unique paired portable display units) and the control device is St. Jude Medical's FFR measuring device, Pressure Guidewire and Analyzer Express. The subjects who met the criteria for this study will be registered by login to the central registration system after enrollment, and the investigational device will first be used to

measure the fractional flow reserve of coronary stenosis lesions, and then the measurement of the same lesions by using the control device will be recorded, and followed with a 48hr post operation follow-up. Control device's FFR (FFRpw) will be used as a reference to statistically analyze Investigational device's diagnostic accuracy, sensitivity, specificity, positive predictive values, negative predictive values, and the Area Under the Curve (AUC) of Receiver Operating Characteristic (ROC). FFR_{ws} and FFR_{pw} will be used to analyze the consistency, also Passing-Bablok regression analysis, Bland-Altman deviation analysis, and Pearson correlation analysis of the FFR_{pw} and FFR_{ws} will be used to evaluate the success rate of the device. Through above analysis, the effectiveness of diagnosis coronary artery disease by using Zurich Medical's pressure guidewire system to measure fractional flow reserve (FFR) can be verified. The adverse event and device defect during the measurement can also be recorded.

4 BACKGROUND INFORMATION

Coronary Artery Disease (CAD) is a type of coronary aortic-like plaque formation, vascular cavity stenosis as a pathological basis, a disease that causes clinical symptoms due to the imbalance of myocardial ischemia and oxygen supply in the corresponding coronary artery supply area. In the past, coronary artery angiography (Invasive Coronary Angiography, ICA) was considered the "gold standard" for the diagnosis of coronary heart disease. However, it can only make a morphological subjective evaluation of the coronary artery and cannot carry out functional evaluation. Dr. Pijls and others in 1993 put forward that functional indicator of stenosis through the fractional flow reserve (FFR) for the evaluation of vascular stenosis, to some extent, make up for the deficiency of coronary artery angiography. When there is a stenosis lesion in the coronary arteries, the ratio of the maximum blood flow to the corresponding heart muscle area range of blood supplied by the target arteries measured by pressure guide is obtained by FFR. In a normal coronary physiological state, the FFR value is1.0, which is not affected by changes in hemodynamic parameters such as heart rate, blood pressure, and myocardial systolic rate.

Subsequently, Dr. Pijls, among others, conducted FFR measurements on 45patients to assess the severity of coronary stenosis leading to myocardial ischemia, use FFR<0.75 as a positive threshold, the results show FFR for diagnosing coronary artery reversibility ischemia has 88% Sensitivity, 100%specificity and 93% accuracy. From early DFFER study to later international multicenter large-sample-size FAME study, FAMEII study, and through long-term clinical practice and research, several studies show that FFR measurements can accurately evaluate coronary ischemic lesions, selectively intervene positively with myocardial ischemic-related lesions, improve patient prognosis, reduce the incidence of

major cardiovascular events. In 2014, Clinical guidelines for myocardial blood reconstructive published by the European Society of Cardiology categorized FFR as IA class，highest recommendation level for when ischemic-related blood vessels are not clear. In 2016, Chinese guidelines for the intervention treatment of coronary arteries suggest for patients with stable coronary heart disease with no evidence of ischemia and with angiography show of stenosis of 50% -90% lesion perform FFR assessment. The suggestion comes with IA class, the highest level of the class.

Current FFR device for intravascular measurements has multiple independent components and bulky monitors, and there has been a need to improve. The high cost of the capital equipment and associated high maintenance costs hinder the spread and adaptation of FFR technology, which is not conducive to the selection and effective evaluation of PCI surgical treatment, and thus to the effective conservation of medical resources and the reduction of national health insurance expenditure.

Zurich Medical invented the device for intravascular measurements in 2013, which is the device and method for intravascular diagnostics. The device comprises a pressure guidewire and a display unit. The pressure guidewire consists of a core wire and a sensor arranged in the distal end of the core wire. The display unit includes a processor and display screen and can receive communication signals from the pressure guidewire. The display unit is configured to use the processor to perform the calculation based on the communication signal received from the pressure guidewire and is configured to display information on the display screen based on the calculation. The display unit can be configured to be disposed of after a predetermined number of uses or after a predetermined period of use. Based on the above invention, the "pressure guidewire system" of medical device devices consists of a self-contained sensor guidewire and a portable processor display unit for measuring the physiological parameters of the coronary artery and peripheral blood vessels and the heart, and can also direct the catheter through the blood vessels.

Zurich Medical's Pressure Guidewire System, which cleverly combines pressure guidewire and processor display unit, uses high-tech sensors to accurately measure blood pressure and offers a variety of options for one or more measurements. Through high-precision low drift pressure detection algorithm, non-electro cardioid heartbeat pressure sensing algorithm and low false positive heartbeat detection filtering algorithm, the blood fractional flow reserve is calculated, and the intuitive display is made in a timely and accurate manner through self-contained portable display unit, which is convenient for doctors to use, easy to operate and with high accuracy. Because there is no need to use any external equipment, ensuring safety and effectiveness at the same time, greatly reduce the cost of surgery, reduce the financial burden of patients, is beneficial for the adaptation of FFR technology at all levels of hospitals, and more conducive to the national health insurance system to save resources.

5 PRODUCT FEATURES, STRUCTURAL COMPOSITION, WORKING PRINCIPLE, FUNCTIONAL MECHANISM AND TRIAL SCOPE

5.1 Product Features

The product is a pressure wire system with self-contained sensor guide and portable processor display unit, it can complete blood pressure measurement without the need for any external device and able to operate independently. The fractional flow reserve (FFR) is calculated through an innovative software design that includes precise algorithms, real-time display of results, greatly facilitate the doctor's operation in the process. Self-contained all-in-one product, small size, easy to operate, no need to buy any external equipment. The product offers two pressure measurement methods, including the AO method and the 1-sensor method, which allows doctors to use different pressure measurement methods to ensure the smooth operation and patient safety according to the actual situation of the patient and the operation.

5.2 Product Structural Composition, Working principle, Functional Mechanism

5.2.1 Structural Composition

The Pressure Guidewire System Model 100 consists of a 0.014" (0.36 mm) diameter, 180 cm long Guidewire with a high-fidelity sensor located immediately beyond the 3 cm shapeable radiopaque tip and a uniquely paired Portable Display (Figure 1). The signals from the sensor can be used to measure blood pressures and estimations of Fractional Flow Reserve (FFR). The Guidewire is connected to the Portable Display via the Handle. The distal end has hydrophilic coating. The Portable Display also has an AO cable that may be used to connect to the Zurich Medical Accessory Cable for AO pressure signal.

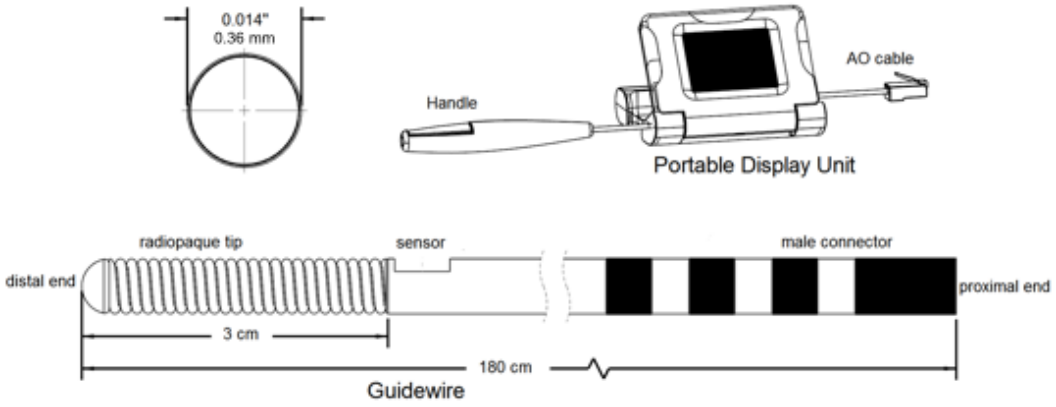
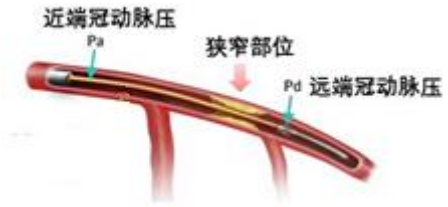


Figure 1: Pressure guidewire system

5.2.2 Working Principle and Functional Mechanism

Fractional Flow Reserve (FFR) based on the principle of anatomy and functional regulation of coronary artery circulation defined as the ratio of the maximum blood flow to the myocardium of the epicardial stenosis coronary artery and the maximum blood flow to the myocardium when the same coronary artery is healthy. It's equivalent to the average pressure of the distal-end of stenosis during a hyperemia state (Pd) and the average aortic pressure during hyperemia state (Pa) (Figure2). Clinically using vessel dilator to induce hyperemia in myocardium, can reduce cardiac microcirculation resistance small enough and become negligible and constant, at this time the myocardial blood flow is only affected by perfusion pressure, so that the reduction of perfusion pressure in the hyperemia state can be equivalent to the degree of narrowness as the heart muscle blood flow is reduced.



FFR: Fractional Flow Reserve

Assess whether stenosis causes myocardial ischemia

The gold standard for clinical assessment whether the stent implantation is necessary

FFR = P_d / P_a (during hyperemia)

FFR>0.8	No interventional treatment required
0.75 < FFR ≤ 0.8	Doctor's assessment
FFR ≤ 0.75	Interventional treatment (implant stent)

Figure 2: The basic principles of calculating fractional flow reserve (FFR)

The product can measure FFR using the conventional AO method, as shown in Figure3.

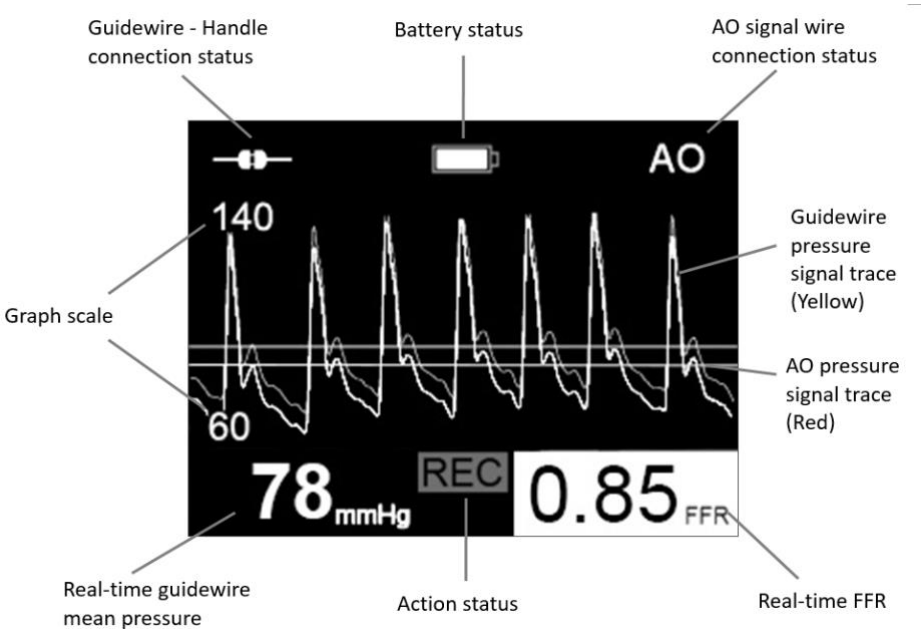


Figure 3: AO Method Real-Time Data Screen

In addition to being able to measure FFR using the above conventional AO method, the pressure guidewire system also provides an innovative1-sensor method for FFR measurement, i.e. measuring at different parts of the vessel using the same sensor. Using the same sensor to measure in different parts of the blood vessel, is more accurate and reduce the error that can be generated by using two sensors. FFR value is automatically calculated and displayed by the precise algorithm provided by the portable display unit in real time. The innovative1-sensor measurement as shown in Figure 4:

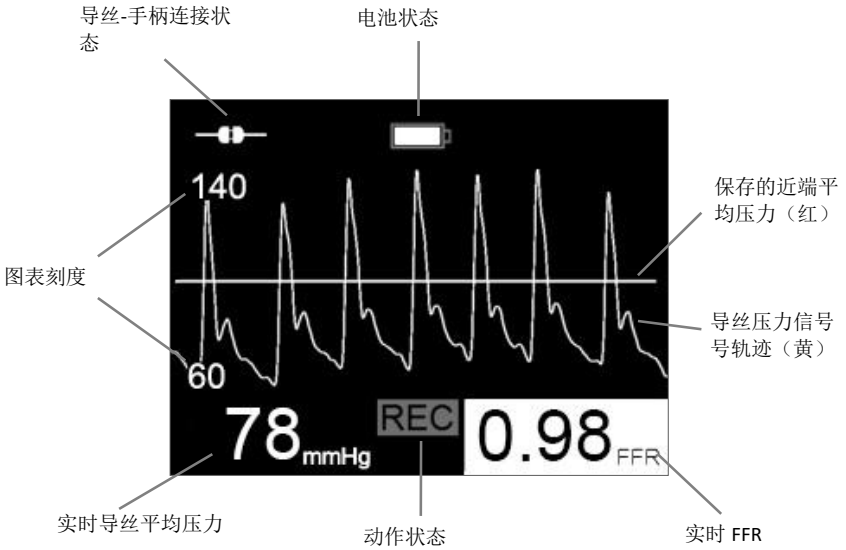


Figure 4:1-Sensor Method Real-Time Data Screen

5.3 Trial Scope

The pressure guidewire system is used to measure coronary blood pressure during diagnostic angiography and/or interventional procedure. The FFR value is automatically calculated by an accurate algorithm provided by the portable display unit in real time to support assessment of ischemic conditions in myocardial lesions.

6 PRODUCT'S INDICATION FOR USE AND CONTRAINDICATIONS, WARNING

6.1 Indication for use

For patients who need coronary angiographic examination and coronary interventional treatment, pressure guidewire system is indicated to calculate the patient's fractional flow reserve (FFR), and to assist the physicians to make clinical decisions.

6.2 Contraindications

The Pressure Guidewire System is contraindicated for use in the cerebral vasculature.

6.3 Warning

1) Pressure Guidewire System is intended for single use only.
2) Do not resterilize or reuse.
3) Do not use if the original sterile package is not intact.
4) Inspect the system carefully prior to use to verify that all parts are present and undamaged.
5) Reuse after cleaning attempts, resterilization and repackaging may result in patient/user infections and compromised product functionality, such as inaccurate pressure signals and inaccurate torque response thereby exposing the patient to increased risks for complications/adverse events.
6) Prior to use and when possible during the procedure, inspect Guidewire carefully for bends, kinks or other damage. Do not readjust any bend or kink as readjustments may damage the electrical wiring inside the Guidewire.
7) Guidewire must not be used if it has been damaged in anyway; otherwise, vessel/ventricle damage and/or inaccurate pressure signals or inaccurate torque response may occur.
8) When introducing Guidewire in a diagnostic case, flush the catheter and

administer an anticoagulant based on standard of care for catheterization procedure or clotting may occur.

9) When the Guidewire is exposed to the vascular system, it should be manipulated while under high-quality fluoroscopic observation. If resistance is met during manipulation, determine the cause of the resistance before proceeding.

10) Do not torque Guidewire without observing corresponding movement of the tip; otherwise vessel/ventricle trauma may occur.

11) Always advance or withdraw Guidewire slowly. Never push, withdraw or torque Guidewire if it meets resistance.

12) Positioning of catheters and guidewires in the ventricles is potentially arrhythmogenic. It should never be done without ECG monitoring and the presence of a functioning defibrillator.

13) Avoid using Guidewire in the ventricles if the patient has a prosthetic mechanical valve. Zurich Pressure Guidewire System may become trapped and disrupt the function of the valve, leading to serious injury or death.

14) Do not use it in the electrosurgical environment when high-frequency surgical equipment is used at the same time.

7 Overall Design

7.1 Trial Design

This study is multi-center, prospective, single-subject design clinical trial. Subjects that signed Informed Consent form (ICF) which was approved by the Ethics Committee (EC) will enter selection process. Subjects that meet all inclusion criteria and do not meet any of the exclusion criteria, are considered eligible to enroll in the clinical trial.

Coronary angiography is performed on subjects. The investigators combine angiographic images and subject's inclusion/exclusion criteria to confirm if the subject meets the trial requirements. The subjects who met the criteria for this study will be registered by login to the central registration system after enrollment, and the investigational device will first be used to measure the fractional flow reserve of coronary stenosis lesions, and then the measurement of the same lesions by using the control device will be recorded, and followed with a 48hr post operation follow-up. The investigational device measure FFR using the innovative 1-sensor method according to the product Instructions for Use (IFU), and the control device measure FFR through the conventional AO method according to the product Instructions for Use (IFU).

7.1.1 Trial Objective

To Evaluate the effectiveness and safety of Zurich Medical's pressure guidewire system (including guidewire with high-fidelity sensors and a unique paired portable display unit), which is used to measure the coronary artery blood fractional flow reserve (FFR) to diagnose coronary heart disease, and the effectiveness and safety of to direct a catheter through a blood vessel. Including:

Effectiveness: Coronary artery Fractional Flow Reserve(FFR) measured by control device, St. Jude Medical's Pressure Guidewire and Analyzer Express (FFRpw) will be used as a reference to evaluate FFR measured by Investigational device, the Zurich Medical pressure guidewire system (including wire with high-fidelity sensor strains and unique paired portable display units) (FFRws)'s efficacy to diagnose coronary artery disease via diagnostic consistency, sensitivity, specificity, positive predictive values, negative predictive value, and Area Under the Curve (AUC) of Receiver Operating Characteristic (ROC). Meanwhile, Passing-Bablok regression analysis, Bland-Altman deviation analysis and Pearson correlation analysis of the FFRpw and FFRws will be used to evaluate the success rate of the investigational device.

Safety: The adverse events and device defects that occur during Zurich Medical's pressure guidewire system measurement of coronary arterial FFRws will be mainly evaluated.

7.1.2 Selection of Trial Method and Justification

The nature of this clinical study is medical device registration clinical validation. Therefore, it is necessary to comply with the relevant regulations such as the "Provisions for Medical Device Registration" and the "Quality Management Practice for Clinical Trials of Medical Devices" promulgated by the CFDA.

7.1.2.1 Reason for selection of the control group

After searching the China Food and Drug Administration (CFDA) medical device database, St. Jude Medical's Pressure Guidewire and Analyzer Express are listed as CFDA approved products. The selection of the control device for this trial is based on the following:

(1) The basic principle and the indication for use of the control device are the same as those of the investigational device;

(2) The control device has been on the market in China and has a wide clinical use, with good clinical effectiveness and safety.

7.1.2.2 Reasons for the selection of the trial population

According to the investigational device's indication for use, the trial population selected in this clinical trial is to perform coronary angiography to determine the

degree of stenosis. Such trial population satisfies the relevant range of indication for use and is representative.

7.1.2.3 Reason for the selection of the endpoints

The primary effectiveness endpoint is the diagnostic consistency of $FFR_{WS,}$ for diagnosis of coronary heart disease measured by Zurich Medical's Pressure Guidewire System.

7.1.3 Measures to Lessen and Prevent Bias

This clinical trial will use the following methods to lessen bias in trials.

Multi-center: Case samples from multiple centers are more representative than single centers, preventing systemic errors in a single center from biasing the trial results, and obtained conclusions are more credible. To reduce the operational differences between the investigational sites, investigators should be trained by uniform standard, and clear evaluation criteria should be adopted for the effectiveness indicators and safety indicators.

Control: This study is a single-subject design clinical trial. Subjects use investigational device then control device to complete FFR measurements, preventing factors that may affect efficacy judgment.

Investigator Training: Before the clinical trial begins, the auditor and the head of investigational site will provide training for investigators, so investigators will gain understanding and become familiar with the investigational device. Investigators should also have grasp on all new findings during the clinical trial that's related to the investigational device.

Clinical Trial Monitoring: Develop inspection plan. Sponsor appoints auditors to conduct regular on-site audit of investigational sites, ensure that all content of the research program is strictly observed, and the original data is checked for consistency with the contents on the EDC.

7.1.4 Investigational Medical Devices and Controlled Medical Devices / Control Methods

The ICA examination performed by qualified interventional cardiologist. After the informed consent form is signed, coronary angiography will be taken from different positions via standard operating procedures. After enrollment, and registration in the central registration system, investigator will first use investigational device to perform FFR measurement, then use control device to remeasure FFR of the same vessel. The interval between two measurements should be greater than 3 minutes. The pressure guidewire

and catheter should be flushed with saline. Nitroglycerin to be used to eliminate coronary artery spasm, and ATP are to be infused through the central vein (intermediate elbow or femoral vein) at 140-180 μg·kg-1·min-1 to place the coronary vessels in hyperemia state. FFR measurements should be performed by qualified, experienced, and trained physicians, primarily focus on stenosis that shows moderately stenotic lesions (diameter stenosis 30% - 70%) in vessels that's ≥ 2.5 mm in diameter. The FFR results from the investigational device and the control device are not be used as a reference basis for further stent therapy. See operational instruction below:

DIRECTIONS TO USE ZURICH PRESSURE GUIDEWIRE SYSTEM 1-SENSOR METHOD TO TAKE MEASUREMENTS:

1） Open the package using sterile techniques

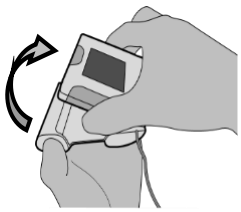
2） Fill the coil with saline solution, using the flush port

3） Soak Guidewire in saline until calibration is complete

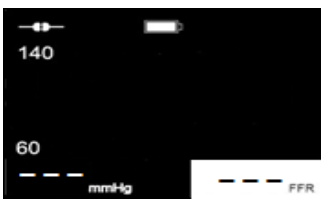
4） Gently detach the portable display unit from the tray

5) Carefully wipe and dry the proximal end of Guidewire and insert into Handle (see Figure 1 for proximal end location of Guidewire)

6） Open the portable display unit by lifting the screen. This turns on the portable display unit



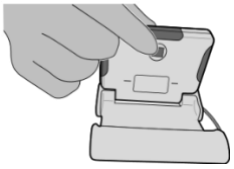
7） Verify the Guidewire -handle connection status icon is displayed in the upper left corner to confirm the correct connection



8) Ensure the tray containing the Guidewire is at the same height as the patient's heart

9） Press the button once for calibrating the system to zero atmospheric pressure (the

button is on the back of the screen). CAL will be displayed in the action state box at bottom center of the display



10）Carefully remove the Guidewire from the package coil

WARNING: Guidewire is a delicate instrument and should be handled carefully. Bending or excessive force during removal from packaging tray may damage the guidewire.

CAUTION: If recalibration is necessary during the case, remove Guidewire from the body and follow the RESET procedure after step 20.

NOTE: After calibration, the Guidewire may be disconnected from the Portable Display for ease of advancement.

11）Engage the guiding catheter using standard practice and flush the catheter with sterile saline solution

WARNING: When introducing the Guidewire, confirm that the catheter tip is free within the vessel lumen and is not touching the vessel wall. Failure to do so may result in vessel trauma upon Guidewire exit of the catheter. Use the radiopaque marker of the catheter to confirm position.

12）Carefully insert the distal tip of the guidewire into the hemostatic valve of the Y connector. Advance Guidewire out of the guiding catheter and steer Guidewire to a location just proximal to the lesion of interest

13）Pull back the insertion tool out of the hemostatic valve and tighten the hemostatic valve

14）If the Guidewire has been detached from the Portable Display, carefully wipe and dry the proximal end and reconnect it now with the Handle. Verify the connection by checking for in the upper left corner of the display

15）If estimating FFR, induce maximum hyperemia using standard clinical practice

CAUTION: Failure to achieve maximum coronary and myocardial hyperemia may result in invalid FFR.

16）Save the pressure proximal to the lesion of interest by pressing and holding the BUTTON until SAV is displayed in the action status box. At this point RELEASE the BUTTON

17）Advance Guidewire across the lesion and perform pressure measurement

WARNING: Observe all Guidewire movements. Whenever Guidewire is moved or torqued, the tip movement should be examined under fluoroscopy.

WARNING: Torque Guidewire against resistance or repeated attempts to cross a total vessel occlusion may cause damage and/or fracture, which may lead to a portion of Guidewire separating from the tip.

CAUTION: Do not measure pressure when the sensor element of Guidewire is in sharp curves, since this might result in pressure artifacts.

NOTE: When a position of interest is difficult to reach, Guidewire may be disconnected from the Portable Display for easier use. Carefully wipe and then dry the male connector before reconnecting to Handle.

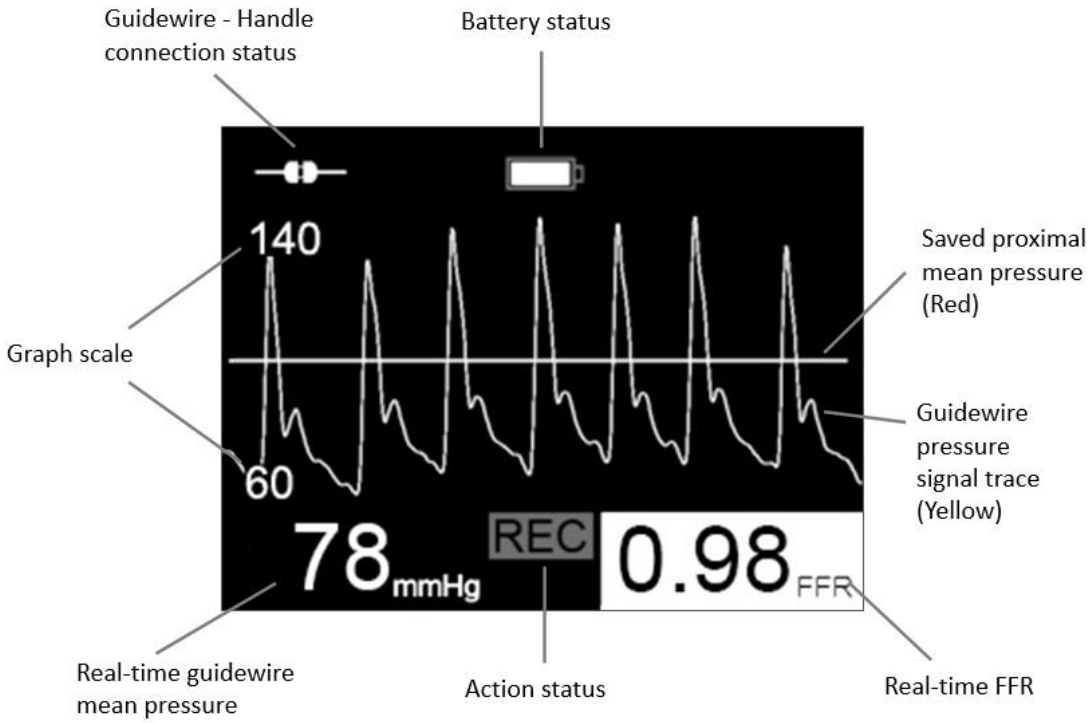
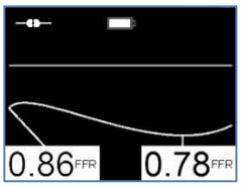


Diagram 3: Live Data Screen 1-Sensor Method

18）Double-click the BUTTON ◎ to begin recording an episode. REC will display in the action status box;

19）Press the ◎ BUTTON again to once to end recording an episode. The data review screen of the episode will appear on the display. The two lowest FFR values will be displayed



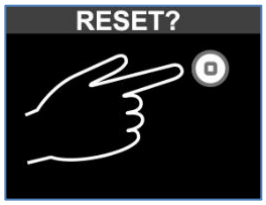
20）Press the BUTTON again once to return to live data screen;

WARNING: Excessive manipulation when sensor element or tip of Guidewire is located in sharp bend may cause damage or tip fracture. If the guiding catheter is in an anatomically severe or sharp bend, for example a tortuous subclavian artery or adjacent vessel position, the junction between the shaft and the flexible distal section of the wire, 31 cm from the tip, may be vulnerable to kinking or fracture.

DIRECTIONS TO RESET

NOTE: If for any reason, the Portable Display needs to be reset and returned to out-of-the-box settings, do the following

1. Press and hold the BUTTON for more than 5 seconds until the RESET screen appears



2. Press the BUTTON again to confirm reset to out of the box settings
3. If an inadvertent BUTTON press for more than 5 seconds occurs, wait until the countdown clock reaches 0 and the portable display will return to the screen before the reset mode is activated

WARNING: Recalibration is required following RESET. Remove Guidewire from the body and follow the instructions above to calibrate.

Use St. Jude Medical 's Fractional Flow Reserve (FFR) Measuring Device to Measure FFR:

1）Connect the power cord, connect the aortic pressure input cable, and turn on the Analyzer Express

2）Select or create a new patient

3）Engage the guiding catheter in accordance with standard procedures and flush the

guiding catheter

4） Place the AO sensor at the same height as the patient's heart, connect the pressure sensor to the air (through the atmosphere), and zero the aortic pressure;

5） Open the pressure guide wire package and leave the pressure guide wire in the tray

6） Fill the packaging coil with heparin saline through the innermost rinse port of the packaging coil

7） Connect the pressure guidewire to the Analyzer Express, and zero the pressure guidewire

8） Gently remove the pressure guidewire from the packaging coil

9） Insert the pressure guidewire into the guiding catheter and advance the pressure guidewire until the pressure sensor just outside of the guiding catheter

10） Equalize the Pd and Pa values

11） Push the pressure guidewire to the distal end of the lesion and record the vessel and position

12） Record the resting Pd/Pa through the pressure guidewire

13） Use standard catheter laboratory procedures for administer nitroglycerin, then adenosine from the vein to achieve hyperemia

14） Record the FFR value through pressure guidewire

15） Retract the pressure guidewire until the sensor just outside of the guiding catheter, the pressure wire position is similar to the position during the equalization of Pa and Pd earlier, and verify that the difference between the aortic mean pressure (Pa) and the pressure guidewire reading of mean pressure (Pd) is within ±3 mmHg. ;

16） Repeat the step 6 – 11 to measure other lesions

17） Remove the pressure guidewire from the body

7.1.5 Subject Selection (including control group selection if necessary)

(1) Inclusion Criteria

Patients must meet all the following inclusion criteria to qualify for enrollment:

1） Age 18 to 75 years old, gender-unrestricted, non-pregnant female;

2） Understand and be willing to sign an informed consent form;

3） Diagnosed with coronary heart disease;

4） Intrusive ICA and FFR measurement are needed;

5） Visual coronary angiography showed at least one moderate stenosis lesion (diameter stenosis of 30% - 70%) on the coronary artery with diameter ⩾ 2.5mm

(2) Exclusion Criteria

Patients meet any of the following criteria is not qualified for enrollment:

1） Patient who do not understand or are unwilling to sign an informed consent form;

2） Has a history of myocardial infarction;

3） Patient with other serious diseases are not suitable for clinical trials, such as a complex congenital heart disease history, severe heart failure(NYHA cardiac function level IV), long QT syndrome, severe hypertension, Severe asthma, severe chronic obstructive pulmonary disease, liver and kidney dysfunction and other serious infections and critical illnesses;

4） Coronary intervention surgery contraindications;

5） Patient with ATP contraindications (ATP contraindications: sinus syndrome, sinus insufficiency and the elderly with cautious use or no use);

6） The clinical manifestations of patients show acute instability, including acute chest pain (sudden appearance), cardiogenic shock, unstable blood pressure (systolic pressure less than 90mmHg), severe congestive heart failure or acute pulmonary edema;

7） The angiography shown or suspect of thrombosis;

8） The angiography shown or suspect of dissection;

9） Left main coronary artery disease, target blood vessels with severe curvature or calcification lesions, total occlusion;

10） There are any other factors that the investigator considers unsuitable for inclusion or completion of this study.

(3) Standards and procedures for terminating trial / trial treatment

Subject may withdraw from the trial at any time during the trial without any reason; and after signing of the informed consent form, subject can still choice not to participate in any trial procedures (by doing so it's equivalent to withdraw the consent). If after signing the informed consent form, the subject chooses not to participate in the trial, investigator must be informed. But no matter what happens, the subject has the right to continue to receive other standard treatments.

The investigators can also withdraw subjects from the trial based on medical judgment at any time.

1) Criteria for the subject to be withdrawn from the trial:

The subject meets any of the following and trail stops:

- The subject withdrew his/her informed consent
- The investigator believes that there are any safety reasons (adverse events or serious adverse events)
- The investigators believe that subject has poor compliance with trial protocol

2) Criteria for terminating the trial:

- Sponsor requests to terminate the trial
- The regulator or the relevant department of the administration requests the termination of the trial
- For the purpose of protecting subject rights and interests, the investigators believe that the subject should terminate the trial
- Subject death

3) Elimination Criteria:

- After enrollment, subject found to not meet the inclusion criteria, or meet exclusion criteria
- Serious breach of protocol (confirmed by the principal investigator).

(4) Enrollment Time

Before the selection, subject's consent and signed informed consent form required

1) Subject's general information, past medical and disease history, examination of combined drug use
2) Physical examination, vital signs, clinical diagnosis
3) After coronary angiography, the investigators combined with angiographic images and subject inclusion/exclusion criteria to determine whether to use the control device and the investigational device to determine identified lesion's FFR, if the

inclusion criteria are met, and no exclusion criteria are met, subject will then be selected for the trail and the time will be recorded for enrollment.

(5) The Expected Overall Duration of Clinical Trial and Rational

The overall duration of clinical trial, including the time of signing clinical trial agreement in all trial hospitals, ethical committee approval and post-conference rectification, filing time, trial initiation, patient enrollment, and FFR procedure time, collection, statistics, and summary of trial data, report creation time, etc., is expected to be 2 years.

(6) The expected duration of each subject's participation

Considering that the time of enrollment and the operation time are the same day, the subjects are required to complete the informed consent form signing, vital signs, physical examination, medical history investigation, and clinical diagnosis within one week before enrollment. Each trial subject's participation time is set at the end of the visit from the time the subject signs an informed consent form, and the expected duration of each subject's participation is no more than 9 days, based on the number of visits set by the clinical trial program.

(7) Number of subjects required for clinical trials

A total of 300 subjects are planned for this trial. Through the results of angiographic images and inclusion/exclusion criteria, investigator will confirm if the subject met the trial requirements and those meets all the qualifications will be enrolled. After enrollment and logged into the central registration system, subject's FFR measurements were performed using a control device after the investigational device to assess the Fractional Flow Reserve of the coronary artery stenosis

7.1.6 Effectiveness evaluation methods

7.1.6.1 Description of effectiveness parameters

(1) Primary effectiveness endpoint:

Diagnostic consistency rate in the diagnosis of coronary heart disease with investigational device and control devices: Each subject will be considered as a research unit (for patients with multiple lesions, the method of converting the results of multiple lesions into patient level is defined in the statistical analysis plan), and the coronary artery FFR_{PW} measured by control device will be taken as reference, when the measurement of control device is

positive ($FFR_{PW} \leq 0.80$) or negative ($FFR_{PW} > 0.80$), the investigational device is also positive or negative.

(2) Secondary effectiveness endpoint

- The sensitivity and specificity of the investigational device used to diagnose coronary heart disease: Taking the subject as the research unit, the sensitivity and specificity of investigational device for diagnosis of coronary heart disease will be calculated. FFR_{PW} of coronary artery measured by control device will be used as the reference and $FFR_{PW} \leq 0.80$ as positive threshold.
- Positive predictive value, negative predictive value and area under working characteristic curve: Taking subjects as research units, FFR_{PW} measured by control device as reference, and $FFR_{PW} < 0.80$ as positive threshold, the positive predictive value, negative predictive value and area under ROC curve (AUC) of investigational device for diagnosis of coronary heart disease will be calculated.
- Passing-Bablok Regression Analysis: Taking the blood vessel as the research unit, Passing-Bablok regression analysis will be used to analyze the FFR_{WS} value of coronary artery measured by the investigational device and the FFR_{PW} value of coronary artery measured by the control device.
- Bland-Altman Deviation Analysis: Taking the blood vessel as the research unit, Bland-Altman deviation analysis will be used to analyze the FFR_{WS} value of coronary artery measured by the investigational device and the FFR_{PW} value of coronary artery measured by the control device.
- Pearson linear correlation analysis: Taking the blood vessel as the research unit, Pearson linear correlation analysis will be used to analyze the FFR_{WS} value of coronary artery measured by the investigational device and the FFR_{PW} value of coronary artery measured by the control device.
- Device success rate: Taking the blood vessel as the research unit, effective FFR_{WS} and FFR_{PW} readings will be used as the criteria to judge the success rate of the devices, and the success rate of the investigational device and the control device will be compared.

7.1.6.2 Methods and time selection for evaluating, documenting and analyzing effectiveness parameters

(1) Primary effectiveness endpoint: the consistency rate in the diagnosis of coronary heart disease with investigational device and control device.

At Visit 2(FFR-ICA examination), record coronary artery FFR_{WS} measured by investigational device and coronary artery FFR_{PW} measured by control device. After all subjects completed the Visit 2, taking the subject as the research unit, the consistency

rate of investigational device for diagnosis of coronary heart disease will be calculated based on FFR_{WS} measured by investigational device. FFR_{PW} of coronary artery measured by control device will be used as the reference and $FFR_{PW} \leq 0.80$ as positive threshold.

Diagnostic consistency rate = (true positive + true negative) / (positive + negative);

Positive and negative respectively correspond to the results of the control device assay (positive when $FFR_{PW} \leq 0.80$, negative when $FFR_{PW} > 0.80$), true positive refers to that when investigational device is also positive at the same time as control device is positive ($FFR_{PW} \leq 0.80$ and $FFR_{WS} \leq 0.80$, true negative refers to that when control device is negative and investigational device is also negative ($FFR_{PW} > 0.80$ and $FFR_{WS} > 0.80$).

(2) Secondary effectiveness endpoint:

- Sensitivity and specificity of investigational device in the diagnosis of coronary heart disease:

At Visit 2(FFR-ICA examination), record the coronary artery FFR_{WS} measured by investigational device and the coronary artery FFR_{PW} measured by control device. After all subjects completed the visit 2, taking the subject as the research unit, the sensitivity and specificity of investigational device for diagnosis of coronary heart disease will be calculated based on FFR_{WS} measured by investigational device. FFR_{PW} of coronary artery measured by control device will be used as the reference and $FFR_{PW} \leq 0.80$ as positive threshold.

Sensitivity = True Positive / Positive;

Specificity = True Negative / Negative;

- Positive predictive value, negative predictive value and area under the working characteristic curve in the diagnosis of coronary heart disease with investigational device:

At Visit 2(FFR-ICA examination), record the coronary artery FFR_{WS} measured by investigational device and the coronary artery FFR_{PW} measured by control device. After all subjects completed the Visit 2, taking the subject as the research unit, the positive predictive value, negative predictive value and area under the working characteristic curve of investigational device for diagnosis of coronary heart disease will be calculated based on FFR_{WS} measured by investigational device. FFR_{PW} of coronary artery measured by control device will be used as the reference and $FFR_{PW} \leq 0.80$ as positive threshold.

Positive predictive value (PPV) = true positive / (true positive + false positive);

Negative predictive value (NPV) = true negative / (true negative + false negative);

ROC curve drawing and AUC calculation: In a two-dimensional coordinate map, set the horizontal x-axis to false positive rate (False Positive Rate, FPR), vertical y-axis is set to true positive (True Positive Rate, TPR). The FFR_{WS} measured by the investigational

device can be obtained from a TPR and FPR based on its performance on the test sample, adjust the diagnostic threshold for $FFR_{WS,}$ get a series of points that are connected in turn (including (0,0) and (1,1) the two points),it is called the ROC Curve of FFR_{WS}. As the name implies, the value of the AUC is the area below the ROC curve. Curve drawing is done by using MedCalc software.

- Passing-Bablok Regression Analysis: After all subjects completed Visit 2(FFR- ICA examination), taking the blood vessel as the research unit, using FFR_{WS} value of coronary artery measured by the investigational device as the vertical y-axis, and the FFR_{PW} value of coronary artery measured by the control device as the horizontal x-axis to perform Linear regression analysis and record regression analysis equation, slope and intercept.

- Bland-Altman Bias Analysis: After all subjects completed Visit 2(FFR- ICA examination), taking the blood vessel as the research unit, Bland-Altman deviation analysis will be used to analyze the FFR_{WS} value of coronary artery measured by the investigational device and the FFR_{PW} value of coronary artery measured by the control device, and draw deviation map. In the two-dimensional rectangular coordinates of Bland-Altman deviation map, the horizontal x-axis of abscissa represents the average FFR of each lesion vessel measured by two devices, and the vertical y-axis of ordinate represents the difference of FFR of each lesion vessel measured by two devices.

- Pearson Linear Correlation Analysis: After all subjects completed Visit 2 (FFR-ICA examination), taking the blood vessel as the research unit, Pearson linear correlation analysis will be used to analyze the FFR_{WS} value of coronary artery measured by the investigational device and the FFR_{PW} value of coronary artery measured by the control device, and the correlation coefficient and P value will be recorded..

- Device success rate: After all subjects completed the visit 2(FFR-ICA examination), taking the blood vessel as the research unit, use the effective FFR_{WS} and FFR_{PW} readings as the criteria for the success of the use of the device to calculate the success rate of the investigational device and the control device. Compare differences in device success rates between groups.

7.1.7 Safety Evaluation Methods

7.1.7.1 Description of Safety Parameters

The occurrence of adverse events and device defects is used as a safety

evaluation index.

7.1.7.2 Methods and Time Selection for Evaluating, Documenting, and Analyzing Safety Parameters

Adverse events were closely observed and evaluated during the screening period and in the trial. Adverse events that need to be recorded are recorded in the adverse event log. Record the time, occurrence, measures, and results of device defects.

7.2 The Trial Process

7.2.1 The Trial Process

Patients who are eligible for this clinical trial will complete screening and enrollment after Visit 1 and Visit 2, and each subject who meets the inclusion criteria and does not meet any of the exclusion criteria will undergo a series of study visits, including Visit 1 (screening period, -7-0 days), Visit 2 (FFR-ICA examination), and visit 3 (48 hours post-surgery follow up). The specific visit process is described as follows:

7.2.1.1 Visit 1(Screening Period, -7 – 0 days)

Subject selection is according to the inclusion and exclusion criteria. This visit needs to complete the following:

1. Subjects will sign an informed consent form;
2. Demographic Information: record the subject's gender, age (date of birth), ethnicity, height, weight and other information;
3. Complete Medical History: inquire and record the subject's past illness, surgical history, current medical history, etc.;
4. Pregnancy Check-up: complete urine pregnancy test, and if positive, complete blood pregnancy test for confirmation;
5. Combined medications: record drug use that may affect device use evaluation;
6. Laboratory examination: including blood routine, liver function, kidney function, myocardial enzyme, etc.;
7. Vital signs: record subject's systolic pressure, diastolic pressure and heart rate;
8. Inclusion/Exclusion Criteria: complete the inclusion criteria item 1 to 4, and exclusion criteria item 1 to 4 and item10;

9. Adverse Events: record adverse events that occurred during screening process.

7.2.1.2 Visit 2 (FFR - ICA examination)

On the day of the operation after the ICA examination, subjects will be selected again based on the inclusion and exclusion criteria. This visit includes:

1. Inclusion/Exclusion Criteria: complete the inclusion criteria item 5, and exclusion criteria item 5 to 9;
2. Vital signs: record subject's systolic pressure, diastolic pressure and heart rate;
3. Device information: distribute device, record device information;
4. Investigational device coronary artery FFR value: record the position of the blood vessel, record the FFR value measured by the investigational device;
5. Investigational device success rate: using effective FFR readings as a success criterion, record the success rate of the investigational device;
6. Control group device coronary artery FFR value: record the position of the blood vessel, record the FFR value measured by the control device;
7. Control group device success rate: using effective FFR readings as a success criterion, record the success rate of the control device;
8. Adverse Events: record all adverse events that occurred during subject's FFR -ICA examination;
9. Device Defects: record device defects that occurred during the use of devices;
10. Combined medications: record the combined drugs used during the trial.

7.2.1.3 Visit 3 (48 hours post-surgery follow up)

1. Laboratory examination: within 48 hours after the procedure, complete the

laboratory examination, including blood routine, liver function, kidney function, myocardial enzyme, etc.

2. Vital signs: including systolic pressure, diastolic pressure and heart rate;
3. Adverse Events: record all adverse events that occurred during subject's FFR - ICA examination;
4. Device Defects: record device defects that occurred during the use of devices;
5. Combined medications: record the combined drugs used during the trial.

7.2.2 Trial Flow Chart

	Visit 1	Visit 2	Visit 3
Procedure Name	Screening period (-7 – 0 days)	FFR - ICA Examination	Follow (48 hours post-surgery follow up)
Sign Informed Consent Form	X		
Demographic Information [1]	X		
Complete Medical History [2]	X		
Pregnancy Check-up	X		
Laboratory Examination [3]	X		X[7]
Inclusion /Exclusion Criteria	X[4]	X[5]	

	Visit 1	Visit 2	Visit 3
Procedure Name	Screening period (-7 – 0 days)	FFR - ICA Examination	Follow (48 hours post-surgery follow up)
Vital Signs [6]	X	X	X
Device Information		X	
Investigational Device Coronary Artery FFR Value		X	
Investigational Device Success Rate		X	
Control Group Device Coronary Artery FFR value		X	
Control Group Device Success Rate		X	
Adverse Events	X	X	X
Device Defects		X	X
Combined Medications	X	X	X

Note:

1. Demographic Information: including gender, age (date of birth), ethnicity, height, weight, etc.
2. Complete medical history: inquire and record the subject's past illness, surgical history, current medical history, etc.
3. Laboratory examination: including blood routine (RBC, WBC, PLT), liver function (ALT, AST), kidney function (BUN, CR), myocardial enzyme (cTNT) / cTNI, CK, CK-MB). The laboratory will accept examination results within 7 days of the signing of the informed consent.
4. Visit1Inclusion/ Exclusion Criteria: complete the inclusion criteria item 1 to 4, and exclusion criteria item 1 to

4 and item10;

5. Visit 2 Inclusion/ Exclusion Criteria: complete the inclusion criteria item 5, and exclusion criteria item 5 to 9

6. Vital signs: record subject's systolic pressure, diastolic pressure and heart rate

7. Visit 3 Laboratory examination completed within 48 hours of surgery. If the cTNT / cTNI and CK-MB exceed the upper limit of normal by 5 times within 48 hours after surgery; if the blood routine and liver and kidney abnormalities are clinically significant within 48 hours after surgery, and the baseline corresponding examination item is normal or abnormal and it has no clinical significance, review and follow up until abnormalities have no clinical significance.

7.2.3 Device Specification

For the use of the investigational device, the sponsor provides the product's Instruction For Use or User Manual and the Investigator's Brochure and conducts sufficient operation training for all the medical staff involved in the trial during the trial preparation phase to ensure operators are proficient in operating the device.

7.3 Monitoring / Audit plan

Pre-Trial monitoring is mainly divided into: distribution of investigational device to clinical trial sites, preparation of research documents, trial personnel and trial training; In-Trial monitoring is mainly divided into: subjects screening, informed consent, and regular visits, documents to be submitted to the hospital and ethics committee, and monitoring of adverse events; Post-Trial monitoring (or before the termination of the trial) is mainly divided into: recovery of investigational devices, EDC data challenge, confirmation of trial document integrity, Ethics Committee notification, AE and SAE review, closure of sites, clinical trial statistical analysis report and clinical report.

The auditor should undergo the necessary training, be familiar with the Good Clinical Practice for Medical Device and relevant regulations. Also, be familiar with the non-clinical aspects of investigational devices in the trial, as well as the clinical aspects of other similar devices, and clinical trial protocol and related documents.

Each clinical site is visited/inspected at least 2-4 times per week, and the frequency of audits is appropriately increased according to the enrollment situation.

The auditor shall follow the GCP principles and supervise the conduct of clinical trials to ensure that clinical trials are strictly implemented according to the protocol. The trial data is true, complete and accurate. Specific responsibilities

include:

(1) Confirm prior to trial start that the investigational site has the appropriate conditions, including staffing and training, laboratory equipment in good working conditions, estimated a sufficient number of subjects, participating investigators are familiar with the trial requirements;

(2) Whether the investigational sites and investigators comply with the approved clinical trial protocol, the Good Clinical Practice for medical device and the relevant regulations before, during and after the trial;

(3) Confirm that each subject signed an informed consent form prior to participating in the trial. Be aware of subject's inclusion criteria and the progress during the trial. Tests that have not been conducted by the investigators, unconducted examination, and whether errors or omissions are corrected should be clearly and truthfully recorded. Confirm revised informed consent form is resigned by subjects prior to the end of follow up visit.

(4) Confirm that all case report forms are correctly filled out and consistent with the original data. All errors or omissions have been corrected or noted and signed and dated by the investigator. The disease type, the total number of cases and the gender, age, and treatment result of each case should be confirmed and recorded;

(5) Document subjects who withdrawal from the study or is non-compliance with the requirements of the informed consent form. Discuss the situation with the investigator;

(6) Confirm that all adverse events and device defects should be recorded, and serious adverse events and major device defects that may cause serious adverse events are reported and recorded within the specified time;

(7) Responsible for monitoring the supply, storage, use, maintenance and handling of medical device samples after the trial;

(8) Ensure that the relevant equipment is regularly maintained and calibrated and documented during clinical trials;

(9) Ensure that investigators receive the latest version of all documents related to clinical trials;

(10) After each audit, a written report shall be sent to the sponsor and investigational site. The report shall state the name of the auditor, the date of the audit, the location of the audit, the content of the audit, the name of the investigator, the completion of the project, problems, conclusions, and corrections to errors, omissions, etc.

8 Statistical Considerations

8.1 Statistical Design, Methodology and Analysis Procedures

8.1.1 Statistical Design (Hypothesis Testing)

This clinical trial is intended to use a prospective, multi-center, single-subject target value design. The main purpose is to evaluate diagnostic consistency rate in diagnosing coronary heart disease by FFRWS measured by investigational device, using FFRPw as the gold standard. Each subject in the clinical trial will provide a pair of test results from both the investigational device and the control device (FFRWS and FFRPw), and the degree of agreement between the two will be used to evaluate the investigational device's performance, using the control product's result as the "gold standard" in the process of comparison (FFRPW≤0.80 as positive，FFRPW>0.80 as negative), evaluating the primary evaluation index ie. accuracy in coronary heart disease diagnosis, applying target values comparison to ensure FFRWS 's result satisfies clinical application requirements, the corresponding statistical hypothesis testing is:

$$H_0 : p_T \le p_0$$
$$H_1 : p_T > p_0$$

pT represents the investigational device's accuracy in diagnosing coronary heart disease, p0 represents the target value.

8.1.2 Statistical Analysis Methods

（1）Descriptive Analysis: Describing qualitative data with frequency and composition ratio description; describing quantitative data with mean, standard deviation, maximum, minimum, median, interquartile range, 25th percentile, and 75th percentile.

（2）Baseline demographics statistical analysis: Mainly based on descriptive analysis, comparing subgroups that may be involved, use likelihood ratio $\chi 2$ test between qualitative groups, use Fisher's exact test when more than 25% of cell frequencies are less than 5; conduct group T-test between normally distributed quantitative datasets; apply Wilcoxon Rank Sum test between non-normally distributed quantitative datasets.

（3）Efficacy analysis: All subjects undergoing a study product review will be included in the analysis (according to the Intention To Diagnostic (ITD)), for the primary efficacy index, in addition to the point estimate for coronary heart disease diagnosis accuracy, the asymptotic normal method and the exact probability method would also be used to make estimates in the 95% confidence interval, comparing the lower bound of the confidence interval with a target value to determine whether the investigational device satisfies clinical application requirements.

（4）Safety evaluation: Adverse events are described by the number and frequency of adverse events; meanwhile, the specific performance, the severity, and the relationship with investigational device of all adverse events will be described in detail.

（5）For primary evaluation indicators, statistical analysis will be conducted with a one-tailed 0.025 significance level, other indicator statistical analysis will be conducted with a two-tailed 0.05 significance level (unless stated otherwise). Statistical analysis is done with SAS®9.4 statistics software.

8.1.3 Statistical Analysis Procedures

Relevant steps in statistical analysis will refer to the provisions of ICH E9 and the relevant guidelines in the "Guidelines for Biostatistics in Clinical Trial" promulgated by the China Food and Drug Administration (CFDA). Meanwhile, all statistical analysis procedures are carried out in strict accordance with the Standard Operating Procedures (SOP) established by the Medical Statistics Department of the National Center for Cardiovascular Diseases.

8.2 Sample Size Calculation

8.2.1 Total Sample Size

A total of 300 patients is planned to be enrolled in this study. Such sample size is determined by a combination of the research hypotheses and the estimates of expected efficacy, calculated according to statistical principles. The calculation of sample size is based on the primary endpoint, i.e., the accuracy in coronary heart disease diagnosis.

Based on literature reports and clinical experiences, the hypothesized coronary heart disease diagnosis accuracy of the investigational device is set at 83%, while the evaluation standard, i.e., the target value is set at 75%, considering a one-tailed 0.025 significance level and that the maximum drop out rate does not exceed 10%, calculated based on statistics principles, a sample size of 300 provides over 90% confidence, to prove that the performance of the investigational device meets clinical trial requirements (exceeding target value). From clinical experiences, the proportion of patients with positive (FFRPW $\leqslant$ 0.80) and negative (FFRPW > 0.80) in the target population is approximately 1:2, test subjects will be included in a continuous selection process until the total sample size is met. Required sample size calculation is:

$$n = \frac{\left[\mu_{1-\alpha}\sqrt{p_0(1-p_0)} + \mu_{1-\beta}\sqrt{p_T(1-p_T)}\right]^2}{(p_T - p_0)^2}$$

In the equation, represents the coronary heart disease diagnosis accuracy in the test group, presents the target value; represents the quantile corresponding to a normal distribution, represents the statistical test's probability for type I error, use 0.025 here, and represents the test's probability for type II error, use 0.2 for calculation (corresponding to the 80% power).

In addition to the above sample size estimation for the primary endpoint, this clinical trial offers respective statistical considerations for the secondary endpoint. Referencing the target population's positive to negative proportion and the total sample size of 300, in the continuous selected sample, about 100 subjects are tested positive by FFRPW$\leqslant$0.80, while about 200 subjects are tested negative by FFRPW$>$0.80. Based on literature reports, set the results from the control device as the gold standard, the sensitivity of the investigational device compared to it is around 86%; the specificity of the investigational device compared to it is around 78%; under the premise that statistical test's two-tailed 0.05 significance level,

current number of positive cases (100) can ensure the error between the sensitivity and the true value of FFRWS is no more than 6.8% (the estimated accuracy is ±6.8%); number of negative cases (200) can ensure the error between the specificity and the true value of FFRWS is no more than 5.7% (the estimated accuracy is ±5.7%); when the observed sensitivity or specificity of FFRWS is higher than the hypothesized, the estimation accuracy will be further improved..

8.2.2 Number of Clinical Trial per Disease and Reasons for Determination

This clinical trial has tough restrictions on the inclusion/exclusion criteria for selected subjects, it can be considered that the current clinical trial is only conducted for a single indication subject, the above 300 subjects belong to the same disease and will not be further divided.

8.2.3 The Maximum and Minimum Numbers of Subjects Per Clinical Trial Institution in a Multi-center Clinical Trial and Reasons for Determination

This clinical trial will take place simultaneously in multiple clinical trial institutions, in theory, the number of centers to be grouped will be evenly distributed to ensure maximum representation. But considering the feasibility and progress of selection, the number of enrollment for each institution will be adjusted according to situations. To ensure the balance of each center's selection scale, the final size for any one specific institution will not exceed 50% of the total sample size.

8.3 Clinical Trial's Significance Level and Power

In this clinical trial, the significance level for the statistical analysis is set at two-tailed 5% (unless specified), the test's power is about 90% (only for primary evaluation indexes).

8.4 Expected Drop Out Rate

In the sample size design process, the maximum drop out rate during the clinical trial is expected to be 10%, such drop out rate includes all reasons that prevent a subject from being selected for primary analysis, usually referred to serious violations of clinical trial protocols as determined by researchers (influencing the primary efficacy analysis). Possible scenarios include: a subject does not meet the inclusion criteria, or meets the exclusion criteria; a subject did not use any test-related products; a subject used third-party products outside of clinical trial or such. All of the above will be included in the total drop out rate.

8.5 Criteria for Qualified/Unqualified Results in Clinical Trial

To determine whether a clinical trial result is qualified or not from a statistical standpoint, it is to test the result with the initial hypothesis testing. For this clinical trial, the primary index is the accuracy in coronary heart disease diagnosis, the test results and the preset target values could be compared to determine if the investigational device meets the requirements for clinical application.

In summary, the determination will be based on the comparison between the investigational device's accuracy in coronary heart disease diagnosis and the preset target value. If the result shows: the lower bound of the 95% confidence interval for the investigational device's accuracy in coronary heart disease diagnosis is greater than 75% (the preset target value), then a positive result is obtained, therefore proving the investigational device meets the requirements for clinical application.

8.6 Standards and Reasons for Terminating Clinical Trial Based on Statistical Reasons

This clinical trial does not have preset interim analysis and corresponding standards for early termination, thus it is not applicable here. All statistical analysis will be performed after the data has been collected, cleaned, and finally locked in.

8.7 Statistical Methods of All Data, Along With Missing, Unused, and Erroneous Data (Including Withdrawals) and the Processing Methods for Unreasonable Data

The statistical analysis processes (procedures) are carried out in strict accordance with the Standard Operating Procedures (SOP) established by the Medical Statistics Department of the National Center for Cardiovascular Diseases. Details can be referred to related documents.

To account for possible missing data in clinical trials, the missing primary endpoint index will be carried over during analysis, the specific carry over procedure will be outlined in the statistical analysis plan, if there exists any missing results, it will be treated as inconsistent in the consistency evaluation. No carry-over processing will be done on other missing index, analysis will be performed on observed data.

Erroneous and unreasonable data will be cleaned in the data cleansing process before statistical analysis. The information of subjects who withdrew from clinical trials will still be included in the final statistical analysis. The specific reasons for

withdrawal of each subject will be described in the statistical report, the missing primary index caused by early withdrawal will be carried over following the above missing value processing method.

8.8 Reporting Deviation from the Original Statistical Plan

The statistical analysis plan needs to be confirmed by the sponsor and the main investigator, and to be finalized before the locking of database. Prior to finalization, adjustments could be made on the initial analysis plan according to the actual situation during clinical trials. In principle, the main analytical principles, methods, and analysis set will not be modified, and all adjustments will be recorded.

8.9 Standards and Reasons for Selecting Subjects to be included in the Analysis

Statistical analysis will be performed upon the following demographics, demographic categorization will be done prior to the statistical analysis, the analysis population in this clinical trial includes:

Full Analysis Set (FAS): collection of subjects selected based on the Intention To Diagnostic (ITD) principles, refers to the dataset of all subjects who participated in the research and used the investigational device.

Per Protocol Set (PPS): the subgroup of the subjects who completed the trial, excluding those who seriously violated the procedure (refers to the trial subjects who violated the selection standard or the exclusion standard, or those lost during the trial).

Safety Set (SS): Use the same definition method as the Full Analysis Set (FAS), therefore the Safety Set will not be defined separately in the analysis.

The analysis of primary efficacy index will be performed on the Full Analysis Set (FAS) and the Per Protocol Set (PPS); in addition, all baseline demographic data and secondary efficacy analysis will be performed on the Full Analysis Set (FAS), the safety evaluation will also be performed on the Full Analysis Set (FAS).

8.10 Exclusion of Special Information during Hypothesis Verification and Its Reasons (If Applicable)

Not applicable.

9 DATA MANAGEMENT

The collection of clinical data was done by using an Electronic Data Capture (EDC) system. The EDC system has undergone rigorous testing and fully meets the requirements of "Good Clinical Practice for Medical Device" and "Clinical Trial Data Management Technical Guidelines". Before the system is officially launched, it is necessary to conduct training tests on relevant users to ensure that the system meets the test requirements. After the official launch, the relevant personnel will get the account number and password. The account is bound to the user's role and permissions. The account information must be properly kept. The account information must not be shared with others or exercise tasks for others.

9.1 DATA COLLECTION

EDC transfers data directly from the client terminal to the server side over the Internet. Without filling out a paper case report form, investigators can complete data collection by entering the source data directly into the EDC system. Investigators are responsible for the quality of the data entered to ensure the authenticity and integrity of the data. The EDC system provides interface printing, allowing investigators to print information on electronic case reports as needed.

9.2 DATA VERIFICATION AND MODIFICATION

The EDC system provides both online and offline verification methods. When the investigator enters abnormal data, the EDC system issues a real-time warning to remind the investigator to check the data. The data administrator performs a logical check on the data held by the server and issues the wrong data in the form of manual challenge through EDC. Investigators need to answer questions posted. The auditor needs to periodically remind and assist the investigator to answer the questions and ensure that each question is handled correctly. The system will record all the questions and the corresponding answers.

9.3 DATABASE LOCK

When all data entry is completed and submitted, all questions are answered, the system enters the soft lock state. The statistician will generate a blind audit report based on this database. If the confirmation data requires no more modified, the sponsor, the data management person in charge, and the statistical person in charge must sign the database lockout form, and the data administrator will complete the database lock operation according to this form. The locked database must not be modified again. If there is an error affecting the main efficacy index or safety indicator, the sponsor, the data management person in charge, and the statistical person in charge must confirm the unlocking

modification and sign the database unlocking form. The data administrator will modify the error data and perform quality control according to the reason of the unlocking. After the error is revised, the sponsor, the data management person in charge, and the statistical person in charge are required to sign the database lockup form again.

10 FEASIBILITY ANALYSIS

10.1 PROBABILITY OF SUCCESS ANALYSIS

A series of tests and researches have been carried out during the development of this product, including laboratory bench tests, animal studies, and human factors research etc. The company has established a strict quality system, established design control procedures for design and development, and formed documents to implement planning and control of the product design and development process. The product has passed the type testing of Shanghai Medical Device Quality Supervision and Inspection Center of the China Food and Drug Administration (CFDA) and has been strictly tested before leaving the factory. There will be no defective products. In addition, the control device has been approved for marketing in the country. In this trial, the investigator will enroll subjects who meet the trial requirements based on the indication for use of the investigational device. The study design meets CFDA requirements.

10.2 PROBABILITY OF FAILURE ANALYSIS

The main causes of treatment failure or poor performance may be related to the following factors: 1) accuracy and proficiency of the operation; 2) inaccurate understanding of indications for use and contraindications; 3) product defects specifically due to manufacturing.

In addition to the above reasons, there may be other unpredictable risks (such as wire breakage) in this trial, leading to trial failure. However, by following this protocol, conduct procedure at a trial institution, adhering to the subjects' inclusion criteria, and closely monitoring the physical condition of the subjects during the procedure can minimize the risk.

11 QUALITY CONTROL OF CLINICAL TRIALS

During the trial, sponsor assigned auditors will conduct on-site audit to ensure that all aspects of the protocol are strictly followed, and trial documents are filled out correctly. Investigators must undergo unified training so to perform recording and judgment criteria with consistency. The entire trial should be carried out under strict operational standard. The investigator should fill in the requirements

according to the medical report form, truthfully, in detail, and carefully record the contents of the EDC to ensure that the case report form is complete, true and reliable. All observations and findings in clinical trials should be verified to ensure data reliability and to ensure that conclusions from clinical trials are derived from raw data. There are corresponding data management measures in the clinical trial and data processing stages.

The original information from this trial, including signed informed consent, products distribution records, relevant laboratory inspection reports, auxiliary examination reports, case records and other relevant records, shall be kept at the investigational site's related hospital for 10 years after the end of the clinical trial. The Sponsor shall keep the clinical trial data until this product is no longer on the market.

12 ETHICAL ISSUES AND INFORMED CONSENT IN CLINICAL TRIALS

12.1 ETHICAL CONSIDERATIONS

This clinical trial complies with the requirements of the Helsinki Declaration of the World Medical Assembly and relevant Chinese regulations, and shall, in accordance with the requirements of the CFDA Order No.25, pass the ethical audit of the investigational site and protect the rights of the subjects of the clinical trial in accordance with the ethical principles stipulated therein, safety and health, as well as privacy.

12.2 REVIEW AND APPROVAL OF THE TRIAL PROTOCOL

Clinical trial protocol must be submitted to the medical Ethics Committee of the investigational site hospital for approval prior to initiate the clinical trial. During the clinical trials, if the protocol is revised, it shall be implemented only after obtaining written approval from the Ethics Committee.

12.3 INFORMED CONSENT PROCESS AND INFORMED CONSENT FORM

The Ethics Committee must approve the drafted ICF. The sponsor provides ICF to each investigational site. To meet specific requirements, the investigational site may modify ICF. Each investigational sites present sponsor with a copy of the ICF approved by the Ethics Committee, as well as a copy of the renewal and permission for the duration of the trial. The original signed and dated ICF by subject is kept by the investigational site for audit and a copy will be given to the subject.

Whenever new information that may affect the patient's consent is obtained,

ICF (and any other written information provided to the subject) is updated. Any such amendments or updates must be reviewed and approved by the Ethics Committee before made available to the subjects.

13 PROVISIONS ON ADVERSE EVENTS AND DEVICE DEFECTS REPORTING

13.1 ADVERSE EVENTS

Definition: Adverse Events (AE), are adverse medical events that occur during clinical trials, whether or not is related to investigational devices.

Grade:

Mild: Subject can tolerate, does not affect diagnosis and treatment, do not requires special treatment, no impact on the subject's health.

Medium: Subject can not tolerate, and requires special treatment, direct impact on the subject's health.

Severe: Endangers subject's life, results in death or disability, requires emergency treatment.

13.2 SERIOUS ADVERSE EVENTS

A serious adverse event is a death or serious deterioration of health during a clinical trial, including a fatal illness or injury, a permanent defect in the body's structure or function, a need for hospitalization or prolonged hospitalization (Except for those who are hospitalized for medical insurance reimbursement, elective surgery, routine treatment of the disease under study or previous diseases without deterioration of the condition, and who are not hospitalized for emergency treatment only, they are recorded in the original medical case report, and no serious adverse events are reported.), medical or surgical intervention to avoid permanent defects in the body structure or physical function; causes fetal distress, fetal death or congenital abnormalities, congenital defects and other events.

13.3 DEVICE DEFECTS

Device defects refer to under normal use of medical device presents the unreasonable risks that may endanger health and life, such as mislabeling, quality problems, malfunctions and so on.

The investigator shall record all adverse events and device defects during the clinical trial, and jointly analyze the causes of the events with sponsor, form a written analysis report includes opinions on continuing, suspending or terminating the trial, The report shall be submitted by the medical device clinical trial management department of the investigational site to its Ethnic Committee for review.

13.4 SERIOUS ADVERSE EVENT REPORTING PROCEDURES, CONTACT INFORMATION

All adverse events that occur during the clinical trials must be truthfully recorded in the adverse event table. The investigators should give targeted treatment and follow-up on adverse events until symptoms disappear or the symptoms stabilize.

In the case of serious adverse events in clinical trials, the investigator shall immediately take appropriate treatment measures on the subjects, and report in writing to the clinical investigational site's medical device clinical trial management department, and notify the sponsor in writing. The medical device clinical trial management department shall report in writing within 24 hours to the appropriate ethics committee, the competent department of food and drug supervision and administration and the health and family planning authorities of the province, autonomous region or municipality directly under the central government where the investigational site is located. In the case of a death, investigational site and investigator should provide the Ethics Committee and the sponsor with all the information they need.

For serious adverse events and device defects that potentially lead to serious adverse events, the sponsor shall report to the food and drug regulatory authority and the health and family planning authorities within 5 working days, and shall inform the other investigational sites and investigators, and through medical device clinical trial management department to inform investigational site ethics committee in a timely manner.

14 PROVISIONS ON DEVIATION FROM CLINICAL TRIAL PROTOCOL AND REVISION OF CLINICAL TRIAL PROTOCOL

14.1 DEVIATION FROM CLINICAL TRIAL PROTOCOL

The investigator is responsible that protocol is not deviated without prior

notice to the implementer and without the approval of the sponsor, and that all actions are in full compliance with all regulation and procedures established by the Ethics Committee. Without the written approval of the sponsor, the investigator may not deviate from clinical trial protocol for any reason, except in case of medical emergency to protect subject's life, physical health, or to avoid significant harm to the subject. If this happens, the investigator must immediately notify the sponsor. All protocol deviations must be reported to the sponsor.

14.2 CLINICAL TRIAL PROTOCOL MODIFICATION PROCEDURE

The deviation of the clinical plan should be reviewed on a regular basis to determine whether a revision of the protocol or termination is necessary. All revisions to the protocol must be agreed by both the sponsor and the investigators of the investigational sites. The reasons for the revision should be recorded.

When investigational sites and investigators changed from the original list, changes can proceed without a formal amendment. The sponsor maintains an updated list and provides it when needed, but the final report must include the final list of investigational sites and investigators.

15 DIRECT ACCESS TO SOURCE DATA, FILES

15.1 DEFINITION

Source data is the original record of clinical findings, observations, and other activities in clinical trials that can be used for clinical trial reconstruction and evaluation.

Source files are printed files, visual files, or electronic files that contain source data.

15.2 PROVISIONS FOR DIRECT ACCESS TO SOURCE DATA AND FILES

The investigator shall truthfully and accurately record and preserve the source data and source documents from the clinical trial, and accept audit by auditors authorized by sponsor and regulatory authorities.

16 FINANCE AND INSURANCE

Before the subjects of this trial are enrolled, the sponsor, investigational sites and investigator shall handle the trial design, the quality control of the trial, the division of responsibilities in the trial, the costs associated with the clinical trial

undertaken by the agent, and the possible injury treatment during the trial. A written agreement was reached on principles and so on.

This trial stipulates that the sponsor shall bear the cost of treatment and the corresponding financial compensation for subject who suffers injury or death related to the clinical trial, except for the damage caused by the fault of the investigational site and its medical staff during the medical treatment. The sponsor has purchased the medical device clinical trial liability insurance for this trial, and the relevant expenses are paid preferentially to commercial insurance. Sponsor will cover the portion of compensation that's not covered by insurance.

17 CONTENTS TO BE COVERED IN CLINICAL TRIAL REPORTS

The clinical trial report follows the relevant requirements of the "Good Clinical Practice for Medical Device" and is written with reference to the "Clinical Trial Report Template for Medical Devices", which includes but is not limited to:

（1） General information;

（2） Summary;

（3） Introduction;

（4） Objective;

（5） Overall Design;

（6） Content;

（7） General Clinical Information;

（8） Investigational Devices and Control Devices / Control Methods for Diagnosis and Treatment methods;

（9） Statistical Design; Method and Analysis Procedures

（10） Clinical Evaluation Criteria;

（11） The Organizational Structure of Clinical Trials;

（12） Ethic Issues;

（13） Results of Clinical Trials;

（14） Adverse Events and Treatment;

（15） Analysis and Discussion of Clinical Trial Results, Indication for Use, Contradiction and Warnings;

（16） Conclusions of Clinical Trials;

（17） Problems and Suggestions for Improvement;

（18） List of Investigators;

（19） Other Information Requiring Clarification;

（20） Investigator and Clinical Trial Site Opinions

18 THE PRINCIPLE OF CONFIDENTIALITY

18.1 PERSONAL DATA AND DATA PROTECTION

All data obtained in clinical trials are protected. Investigators must not disclose patient's name and other personal data (excluding date of birth/age and gender).

It is important to ensure that the EDC or other documents (ex: report on special findings) transmitted to the National Cardiovascular Center do not contain patient name, but only the patient's registration number (patient number, date of birth, and/or registration number).

Similarly, statistical storage and evaluation can only be performed under the patient registration number. Only the investigator can identify the patient's name/other personal details by registration number.

During clinical trial, if patient's name needs to be identified for medical reasons, all relevant personnel are obliged to keep it confidential.

Personal data storage and process should comply with data protection laws

18.2 CONFIDENTIALITY

All persons involved in this clinical trial should treat the objective and content of this clinical trial and its results as confidential.

The investigators shall keep all the information provided by the sponsor confidential and safe.

Ownership of all documents, test data and results of this clinical trial belongs to Zurich Medical, and no party is allowed to disclose this clinical trial related information without the written permission from the sponsor.

19 AGREEMENT ON THE PUBLICATION OF TRIAL RESULTS

The result of this trial will be used by the sponsor for CFDA product registration and approval. Before the sponsor obtains CFDA product approval, the investigators of each investigational site may not publish any articles based on the clinical trial. To publish article, sponsor's written consent must be obtained. After sponsor obtained

CFDA's product approval, the investigator of each investigational site may publish the article individually, but the data and results of the published article must be consistent with the final clinical report and investigational site report, and sponsor must be notified in writing.

20 RESPONSIBILITIES OF ALL PARTIES

20.1 THE RESPONSIBILITIES OF THE SPONSOR

（1） The sponsor is responsible for initiating, applying, organizing and supervising clinical trials, and is responsible for the authenticity and reliability of clinical trials.

（2） The sponsor is responsible for organizing the development and revision of the investigator's manual, clinical trial protocol, informed consent form, case report form, relevant standard operating procedures and other relevant documents, and is responsible for organizing the training needed for clinical trials.

（3） The sponsor shall select the investigational sites and its investigators from qualified healthcare institutions according to the characteristics of the investigational device used in the trial. Prior to signing the clinical trial agreement, sponsor should provide the investigational site and investigators with the latest investigator's manual and other relevant documents for their decision on whether they can undertake the clinical trial.

The investigator's manual should include the following information:

1) General information of the sponsor and the investigator;

2) Investigational devices summary

3) Rationale for the intended use and clinical trial design

（4） The sponsor shall not exaggerate the mechanism and efficacy of investigational devices used in the clinical trial.

（5） During the clinical trial process, when the sponsor receives important information affecting clinical trial, the investigator's manual and related documents shall be promptly revised and submitted to the Ethics Committee for review and approval through the investigational site clinical trial management department.

（6） The sponsor shall enter into a written agreement with investigational sites and investigators on the following matters:

1) Conduct clinical trials in accordance with relevant laws and regulations and clinical trial protocol, and accept inspection, verification and audit;
2) Follow data logging and reporting procedures
3) Keep the basic documents relating to the trial not less than the statutory time until the sponsor notifies the investigational sites and the investigators the documents are no longer required;
4) After sponsor has obtained the approval of Ethics Committee, it's responsible to provide investigational devices to investigational sites and investigators, and ensure transport conditions, storage conditions, storage time, expiration date, etc.
5) Investigational devices should be of good quality and covered with easy to identify label that reads "Trial Use", and is properly packaged and stored in accordance with the clinical trial protocol;
6) The sponsor shall develop clinical trial quality control related standard operating procedures, such as the transport, reception, storage, distribution, treatment, recycling of investigational device, for investigational sits and investigators to follow.

（7） The sponsor is responsible for the safety of investigational devices in clinical trials. When subject's safety is of concern or that the implementation of the trial may alter the ethics committee's approval of the continuation of the trial, the sponsor shall immediately notify all investigational sites and investigators and respond accordingly.

（8） If the sponsor decides to suspend or terminate the clinical trial, it shall notify all investigational site's medical device clinical trial management department within 5 days and explain the reasons in writing. The clinical trial management department of the investigational site shall promptly notify the appropriate researchers and ethics committees. Suspension of clinical trials may not be resumed without the consent of the ethics committee. After the end of the clinical trial, the sponsor shall inform the food and drug supervision and administration department of the province, autonomous region or municipality directly under the Central Government in writing.

（9） The sponsor shall ensure that all investigators carrying out clinical trials strictly follow the clinical trial protocol, and if they find that investigational sites and investigators do not comply with relevant laws and regulations, this clinical trial protocol, they shall point out and correct them in a timely manner; and if serious non-compliance or persistence happens, the sponsor shall terminate the clinical

trial and report to the food and drug regulatory departments of autonomous regions and municipalities directly under the Central Government where the investigational site located and the CFDA.

（10） The sponsor shall bear the cost of treatment and the corresponding financial compensation for the treatment of the subject who has suffered the injury or death in connection with the clinical trial, except for the damage caused by the fault of the medical institution and its medical personnel in the medical treatment.

（11） The sponsor shall assume the responsibility for supervision and inspection of clinical trials and select the auditor who meets the requirements to perform the supervision duties. The number of auditors and the number of monitors depends on the complexity of clinical trials and the number of clinical trial investigational sites.

（12） The auditor shall have the corresponding professional background of clinical medicine, pharmacy, biomedical engineering, statistics and other relevant professional background, undergo the necessary training, be familiar with the medical device clinical trial management regulations and relevant regulations. Also, be familiar with the non-clinical aspects of experimental devices in the trial, as well as the clinical aspects of other similar devices, and clinical trial protocol and related documents.

The auditor shall follow the standard operating procedures of the clinical trials for investigational devices for testing medical devices formulated by the sponsor, and urge clinical trial to be carried out in accordance with the protocol. Specific responsibilities follow the relevant national regulations and the requirements of the sponsor.

（13） In order to ensure the quality of clinical trials, sponsors can organize auditors who are independent of clinical trials and have appropriate training and experience to audit the conducting of clinical trials and evaluate whether clinical trials meet the requirements of the trial protocol.
Audit can be used as part of the sponsor's routine work on quality management of clinical trials, as well as to assess the effectiveness of audit activities, or to be carried out aiming at serious or repeated clinical trial protocol deviations, suspected fraud, etc. The auditor should develop a audit plan and audit procedure based on the importance of the clinical trial, the number of

subjects, the type and complexity of the clinical trial, the risk level of the subject, etc.

（14） For serious adverse events and defects in devices that may lead to serious adverse events, the sponsor shall report to the food and drug regulatory authority and the health and family planning authorities within 5 working days of learning of the event, and shall inform the other investigational sites and investigators involved in the trial, and through investigational site's medical device clinical trial management department to inform the investigational site's ethics committee in a timely manner.

（15） If the sponsor adopts an electronic clinical database or a remote electronic clinical data system, it should ensure that the clinical data is controlled, truthful and form a comprehensive verification document.
For multicenter clinical trials, the sponsor should ensure that documents are in place prior to the clinical trial to clearly coordinate the division of responsibilities between the investigators..

For multicenter clinical trials, the sponsor shall organize the development of standard operating procedures in accordance with the protocol, and organize operation and maintenance of investigational device training for all investigators, so as to ensure consistency in the implementation of clinical trial protocol and the use of investigational devices.

In this multicenter clinical trial, the sponsor should ensure that the case report form is designed in a rigorous and reasonable manner, enabling the coordinating investigator to obtain all data from the investigational sites..

20.2 RESPONSIBILITIES OF INVESTIGATIONAL SITES AND INVESTIGATORS

（1） Before accept to participate in the clinical trial, the investigational site shall evaluate the relevant resources according to the characteristics of the investigational medical device to determine whether to participate in the clinical trial.

（2） The investigational site shall properly maintain the clinical trial records and basic documents in accordance with the agreement with the sponsor.

（3） The investigator in charge of clinical trials shall meet the following requirements:

1. In the investigational site with deputy director physician, associate professor, associate researcher and other deputy senior professional and technical titles and qualifications;
2. Have the expertise and experience required for investigational medical devices, and should be trained if necessary;

3. Be familiar with the requirement of the sponsor and the information and literature provided by the sponsor and related to the clinical trials,

4. Have the ability to coordinate, to control and use the personnel and equipment to conduct the trial and to be able to handle adverse events and other events related to the investigational device;

5. Be familiar with relevant laws, regulations and this protocol

（4） Prior to a clinical trial, the medical device clinical trial management department of investigational site shall cooperate with the sponsor to submit an application to the ethics committee and submit the relevant documents in accordance with the provisions.

（5） The investigators shall ensure that the relevant staffs involved in the trial are familiar with the principles of operation, indication for use, operating methods, installation requirements and technical specifications of the investigational medical device, the preclinical research data and safety data of the investigational medical device, and the prevention method for potential risks and emergency treatment methods during clinical trials.

（6） The investigator shall ensure that all clinical trial subjects are fully aware of the clinical trial protocol, regulations, characteristics of the investigational medical device and responsibilities associated with the clinical trial, and that there are sufficient numbers of subjects who meet the inclusion criteria and that there is sufficient time during the agreed trial period, to safely implement and complete clinical trials in accordance with the relevant regulations.

（7） The investigator shall ensure that the investigational medical device is used only by the subjects in the clinical trial and shall not charge any fees.

（8） The investigator shall strictly follow the clinical trial protocol, and shall not deviate from the protocol or substantially change the protocol without the consent of the sponsor and the ethics committee, or without the approval of the China Food and Drug Administration in accordance with the provisions. However, in cases of immediate danger, such as the immediate risk of the subject, it may also be allowed to report in writing afterwards.

（9） The investigators are responsible for recruiting subjects and talking to subjects or their guardians. It is the responsibility of the investigator to explain to the subject about the details of the investigational medical device and the clinical trial, and to inform the subject of the possible benefits and known and foreseeable risks, and to obtain an informed consent form signed and dated by the subject or his or her guardian.

（10） Investigators or other persons involved in the clinical trial should not force or other improperly induce subject to participate in the clinical trial.

（11） When the investigators discover adverse events in clinical trials that are not expected from the investigational medical devices, they shall, together with the sponsor, modify the relevant contents of the informed consent form, submit to be reviewed and approved by ethnics committee, and have the affected subject or their guardians re-sign the revised informed consent form.

（12） The investigator is responsible for making medical decisions related to clinical trials, and when adverse events related to clinical trials occur, investigational site and investigators should ensure adequate and timely treatment provided to the subjects. The investigators shall notify the subjects once they become aware of the need for treatment of complications.

（13） In the case of serious adverse events occur during clinical trial, the investigator shall immediately take appropriate treatment measures on the subject, and report in writing to the medical device clinical trial management department of investigational site and notify the sponsor in writing. The medical device clinical trial management department shall report in writing within 24 hours to the appropriate ethics committee and the competent department of food and drug administration and administration of the province, autonomous region or municipality directly under the central government where the investigational site is located. In the case of a death, investigational site and investigators should provide the ethics committee and the sponsor with all the information they need.

（14） The investigator shall record all adverse events and device defects during the clinical trial, and jointly analyze the causes of the events with the sponsor, form a written analysis report, and submit opinions on continuing, suspending or terminating the trial, which shall be submitted by the medical device clinical trial management department of the investigational site to the ethics committee for review.

（15） The investigator should file clinical data reports in accurately, completely, clearly and in a timely manner. The case report form is signed by the investigator, and any changes to the data should be signed and dated by the investigator, while the original records are kept and the original records should be clear and legible.

（16） Investigational sites and investigators should ensure that the data, documents and records formed in clinical trials are true, accurate, clear and safe.

（17） Investigational sites and investigators shall accept the monitoring and auditing by the sponsor and the supervision by Ethics Committee, and provide all required records relating to the clinical trial. When the food and drug administration and the department of health and family planning send inspectors to carry out inspections, the investigational site and investigators shall cooperate.

（18） When investigational site and investigators reach a conclusion that the risk exceeds the likely benefit, or that results are sufficient to determine the safety and efficacy of a

medical device, trial needs to be suspended or terminated. Subject shall be notified and properly treated and followed up, and that detailed written explanations are provided in accordance with report. If necessary, report to the food and drug administration department of the province, autonomous region or municipality.

When investigators receive notification of trial suspension or termination from sponsor or ethics committee, they need to notify subjects in a timely manner and ensure that the subject is properly treated and followed up.

（19） The investigational site or investigators need to report any requests from sponsor that violates the relevant provisions to change the clinical trial data or conclusions, to the provincial, autonomous region or municipality food and drug administration or to the China food and drug administration.

（20） At the end of a clinical trial, the investigator should ensure that records and reports are completed. At the same time, the investigators should ensure that the investigational medical devices received are in accordance with the quantities used, discarded or returned, and that the remaining investigational medical devices are properly handled and documented.

（21） According to the needs of clinical trials, investigators may authorize the appropriate personnel to recruit the subjects, communicate continuously with the subjects, record clinical trial data, manage investigational medical devices, etc. The investigator shall conduct relevant training on authorized personnel and create appropriate training documentations.

20.3 OTHER RESPONSIBILITIES BY OTHER PARTIES CAN BE FOUND IN THE CLINICAL TRIAL AGREEMENT

References

"Helsinki Declaration"

"Regulations for the Supervision and Administration of Medical Devices" (Decree No.650 of State Council) 2014.06.01

"Provisions for Medical Devices Registration" (Order No.4 of China Food and Drug Administration) 2014.10.01

"Good Clinical Practice of Medical Devices" (Order No.25 China Food and Drug Administration, Health and Family Planning Commission of the People's Republic of China) 2016.06.01

"Guidelines for the Design of Clinical Trials of Medical Devices" (No. 6 of 2018) 2018.01.08

"Provisions for Medical Device IFU and Labeling" (Order No.6 of China Food and Drug Administration) 2014.10.01

"Provisions for Supervision of Medical Device Manufacture" 2014.10.01

"GB/T191-2008 Packaging Storage and Transportation Graphic Mark" 2008.10.01

"GB9706.1-2007 Medical Electrical Equipment Part1: General Requirements for Safety" 2008.07.01

"YY0505-2012 Medical Electrical Equipment Part 1-2: General Requirements for Safety –Collateral Standard: Electromagnetic Compatibility – Requirements and Tests" 2014.01.01

"YY0783-2010 Medical Electrical Equipment Part 2-34: Particular Requirements for the Safety, including Essential Performance, of Invasive Blood Pressure Monitoring Equipments" 2012.06.01

"YY0450.1-2003 Accessory Devices for Sterile Single-use Intravascular Catheters Part1:Introducers" 2003.09.01

"GB/T16886.1-2011 Biological Evaluation of Medical Devices Part1: Evaluation and Testing within a Risk Management Process" 2011.12.01

The investigators statement

I agree:

1. This clinical trial will be conducted in strict accordance with the requirements of the Helsinki Declaration, china's existing regulations, and this trial's protocol.
2. Record all required data accurately in the Electronic Data Collection System (EDC) and complete clinical trial reports on time.
3. Investigational medical devices are used only for this clinical trial, and the receipt and use of investigational medical devices are fully and accurately recorded during the clinical trial, and records are maintained.
4. Allow the CRA and auditor authorized or dispatched by the sponsor, and the inspector from regulatory authorities, to monitor, audit and inspect the clinical trial.
5. Strict performance of the terms of the clinical trial contract/agreement signed by the parties.

I have read all the entire clinical trial protocol, including the above statement, and I agree with all of the above.

Sponsor's opinion Signature (stamp) Year /Month/Date
Agent's opinion Signature (stamp) Year /Month/Date
Investigator's opinion Signature (stamp) Year /Month/Date

Investigational site's opinion Signature (stamp) Year /Month/Date