A Multi-Center, Prospective, Observational Registry for the Evaluation of Coronary Artery Calcified Nodules Using Intravascular Ultrasound (IVUS) and/or Optical Coherence Tomography (OCT) in China (CN-IVI Registry)

Brief title: Intravascular imaging evaluated Calcified nodule China Registry

CN-IVI Registry

Verson 2.0 ——Sep/20/2025

Sponsor

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China

II. Investigator Signature Page

Study Title:
Intravascular Imaging Evaluation of Calcified Nodules: A Chinese Registry Study

Abbreviation:
CN-IVI Registry

Version:
1.0, June 10, 2024

We have read this protocol and/or amendments and appendices and agree to comply with the requirements. We will provide copies of this protocol and all relevant information to the personnel under our supervision. We will discuss these materials with them and ensure their full understanding.

We undertake to conduct the study in accordance with this protocol, adhering to its requirements, relevant ethical and safety considerations, and guidelines. The study will be registered following ISO 14155:2020 and applicable regional regulatory requirements.

Investigator Name and Title
Name and Full Address of Site

Investigator Signature
Date (YYYY-MM-DD)

III. Protocol Summary

Study Title
Intravascular Imaging Evaluation of Calcified Nodules: A Chinese Registry Study

Study Abbreviation
CN-IVI Registry

Study Type
Prospective, observational, multicenter, single-arm registry study

Trial Registry
ClinicalTrials.gov

Background
Calcified nodules are a type of coronary calcified lesion. Based on morphological features, they can be classified into two types: those with a crater-like appearance (eruptive morphology) lacking a complete fibrous cap and sometimes accompanied by thrombus adhesion, which may be more closely associated with poor prognosis; and those with a non-eruptive morphology, typically covered by an intact fibrous cap. The natural course of calcified nodules and the selection of optimal treatment strategies require further clarification through large-scale clinical studies.

Objectives

1. To observe the natural course of calcified nodule lesions evaluated by intravascular imaging.
2. For cases undergoing interventional treatment, to evaluate the impact of different treatment strategies on clinical outcomes.

Study Design
The IVI CN China Registry is a prospective, observational, multicenter, single-arm registry study. Patients scheduled for PCI in the catheterization laboratory will undergo intravascular imaging based on the operator's clinical judgment, following standard medical practice. If calcified nodules are detected via intravascular imaging, patients will be further approached for informed consent to participate in the registry. The study plans to enroll 500 patients with coronary calcified nodules evaluated by intravascular imaging. Enrolled patients will be followed for up to 3 years.

Study Centers

Study Centers
Approximately 20 research centers across China

Study Plan
Clinical observation of cases with calcified nodules evaluated by intravascular imaging

Reference Studies
None

Inclusion Criteria

1. Patients must be ≥18 years of age.
2. At least one calcified nodule lesion identified by coronary intravascular imaging.
3. Patients are willing and able to comply with study procedures and follow-up until the study concludes.
4. Subjects confirm understanding of the study risks, benefits, and alternative treatment options, and provide signed informed consent approved by the Ethics Committee before any protocol-related procedures are performed.

Exclusion Criteria
Contraindication to Procedure: Known contraindication to coronary angiography, PCI, or adjunctive pharmacologic therapy (e.g., aspirin, P2Y12 inhibitors, heparin, contrast media) that cannot be adequately managed with standard medical care.

Life Expectancy: Life expectancy of less than 1 year due to non-cardiac comorbid conditions (e.g., active malignancy, advanced organ failure).

Inability to Follow-Up: Inability or unwillingness to comply with the study protocol or scheduled follow-up visits.

Screening and Informed Consent for Patients with Calcified Nodules

- Patients with indications for angiography and potential PCI will be screened according to the inclusion/exclusion criteria.
- After selective angiography, it will be determined whether intravascular imaging is required. Upon completion of intravascular imaging, if at least one calcified nodule is diagnosed, informed consent will be obtained from the patient.
- The decision to treat the nodule and the treatment strategy will be at the operator's discretion.
- Planned angiographic follow-up is discouraged. If clinically indicated angiographic follow-up is performed, it must be documented in the eCRF.

Non-Study Drug Therapy

- Dual antiplatelet therapy, intraoperative anticoagulation regimens, and the use of GP IIb/IIIa inhibitors will be determined by the operator based on the clinical situation.

IVI Core Lab Assessment and Angiographic Collection

- All intravascular imaging data will be collected via a secure electronic transmission system.
- Post-PCI imaging for all subjects will be reviewed by an independent intravascular imaging core laboratory and evaluated according to optimization standards. Feedback will be provided to the clinical trial center when necessary.
- Angiographic images at baseline and during the procedure (including staged procedures if required) for all revascularizations will be collected via a secure electronic transmission system.
- Intravascular imaging and/or coronary physiology data will be assessed by the core laboratory for subsequent subgroup analyses.

Study Endpoints

Primary Endpoint:
TVF (Target Vessel Failure) is defined as the composite of cardiac death, target vessel myocardial infarction*, or clinically indicated target vessel revascularization.

*Periprocedural myocardial infarction will be defined according to ARC-2 but will not be included in the primary composite endpoint. Spontaneous myocardial infarctions (>48 hours post-procedure) will be classified according to the Fourth Universal Definition of Myocardial Infarction.

Key Secondary Endpoints:

1. Composite of target vessel myocardial infarction* and clinically indicated target vessel revascularization.
2. Clinically indicated target vessel revascularization.
3. Composite of cardiac death and target vessel myocardial infarction*.
4. Target lesion failure, defined as the composite of cardiac death, target vessel myocardial infarction*, or clinically indicated target lesion revascularization.
5. Target lesion revascularization.
6. Cardiac death.

* *Periprocedural myocardial infarction will be defined according to ARC-2 but will not be included in the composite endpoint. All myocardial infarctions occurring >48 hours after the procedure will be classified as spontaneous myocardial infarctions according to the Fourth Universal Definition of Myocardial Infarction.*

Other Clinical Endpoints:

1. **Patient-oriented Composite Endpoint (PoCE):** Defined as all-cause death, stroke, myocardial infarction*, and any revascularization.

2. **Device-oriented Composite Endpoint (DoCE):** Defined as cardiovascular death, target vessel myocardial infarction*, and clinically indicated target lesion revascularization.
3. **Target vessel revascularization.**
4. **Stroke.**
5. **Definite and probable stent thrombosis.**
6. **Periprocedural myocardial infarction.**

Periprocedural myocardial infarction will be defined according to ARC-2 but will not be included in the composite endpoint. All myocardial infarctions occurring >48 hours after the procedure will be classified as spontaneous myocardial infarctions according to the Fourth Universal Definition of Myocardial Infarction.

Procedure-Related Endpoints:

1. Procedure duration.
2. Total contrast agent volume used.
3. Device utilization.

Other Procedural Safety Endpoints:

1. Acute kidney injury.
2. Vascular access site complications.
3. Bleeding events.
4. Major intraprocedural complications, including Type C-F dissection, perforation, persistent slow-flow/no-reflow, acute lumen closure, distal embolization, thrombosis, and major side branch occlusion (lumen diameter ≥2 mm).
5. Perforation events according to the Ellis criteria.

Core Laboratory Report:

1. Intravascular imaging evaluation results.

Study Timeline

- Preparation period: 6 months
- Enrollment period: 18 months
- Follow-up period: 24 months
- Close-out period: 6 months
- Total study duration: 54 months

Follow-up Plan
Clinical follow-ups will be conducted at 6 months, 1 year, 2 years after enrollment.

Statistical Analysis

The primary endpoint, Target Vessel Failure (TVF), will be analyzed as a time-to-event endpoint in the Full Analysis Set (FAS) of all enrolled subjects, following the intention-to-treat (ITT) principle. Data will be analyzed using two distinct approaches.

Sample Size
A total sample size of 520 subjects is planned, with a maximum of 130 subjects (25%) per center.

Study Visit Schedule

Item	Screening	PCI Procedure [12]	Post-PCI (Within 24 hours or before discharge)	6 Months (±30 days)	1 Year (±30 days)	2 Years (±30 days)
Visit Method	Site Visit	Site Visit	Site Visit	Phone Visit	Phone Visit	Phone Visit
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Demographics & Vital Signs [1]	X					
Medical & Cardiac History	X					
Lab Results Collection [2]	X		X^3			
12-Lead ECG	X^4		X^5			
LVEF & Valvular Disease [6]	X					
Cardiac-Related Medications	X	X	X	X	X	X
Angina Grade (CCS)	X^7		X	X	X	X
Enrollment	X^8					
Angiography	X	X^9				
IVI Data Acquisition	X^{10}					
Procedure-Related Endpoints	X	X				
Device Deficiencies	X					
Adverse Event Reporting [11]	X	X	X	X	X	X

Item		Screening	PCI Procedure	[12]	Post-PCI (Within 24 hours or before discharge)	6 Months (±30 days)	1 Year (±30 days)	2 Years (±30 days)
Serious Adverse Event Reporting	[11]	X	X		X	X	X	X

Footnotes (Detailed):

1. **Demographics and vital signs** (age, gender, weight, height, blood pressure, heart rate, body temperature, and respiratory rate) must be collected within **72 hours prior to the PCI procedure**.
2. **Laboratory test results** (including white blood cell count, platelet count, hemoglobin, hematocrit, serum creatinine, and cardiac biomarkers) should be collected within **28 days prior to the PCI procedure**.
    - For cardiac biomarkers, **troponin is prioritized**. If available, **CK-MB should also be collected** during the clinical course. Collect all cardiac biomarkers available at the research site.
    - For **clinically stable patients**, collect cardiac biomarkers within **72 hours before PCI**; for **clinically unstable patients**, collect within **24 hours before PCI**.
    - If cardiac biomarkers are elevated before PCI and a second pre-PCI measurement is performed, collect these data as well. If data within the specified time frame are unavailable, collect the most recent available values.
3. **Cardiac biomarkers must be collected within 24 hours after PCI**. In patients with elevated post-PCI cardiac biomarkers, **serial measurements are strongly recommended until a decline is observed**. However, serial measurements are not mandatory if not indicated per local practice.
4. **12-lead ECG** must be performed within **24 hours before PCI** (or within **72 hours for clinically stable patients**).
5. **12-lead ECG** must be performed within **24 hours after PCI or before discharge**.
6. **Left ventricular ejection fraction (LVEF) and valvular disease status** should be recorded if relevant information (e.g., CT, ultrasound, MRI, ventriculography) is available within the **past 90 days** or during the current hospitalization.
7. **Canadian Cardiovascular Society (CCS) angina grade** should be assessed within **7 days before PCI**.
8. **Enrollment** occurs after:
   (1) Informed consent is obtained,
   (2) Eligibility is confirmed,
   (3) Intravascular imaging (IVI) evaluation is completed.
9. For patients undergoing repeat angiography and intravascular imaging during follow-up (except those undergoing revascularization), additional angiographic and IVI data should be collected.
10. **IVI data must be submitted centrally to Cardialysis via AGMedNet no later than 4 weeks after the procedure**.

11. **(S)AE reporting** starts from formal enrollment and continues through the last follow-up. **All intraprocedural (S)AEs must be reported**. For events requiring revascularization, submit angiograms of the event vessel and all prior angiograms to Cardialysis via AGMedNet.

Note:

- *X*indicates the time point(s) at which the procedure/data collection should be performed.
- All timelines (e.g., ±30 days for follow-up) should be strictly adhered to unless clinically justified.
- Local regulations and ethical guidelines must be followed throughout the study.

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1. Introduction

1.1 Background

Calcified nodules are a type of coronary calcified lesion. Based on morphological characteristics, they are classified into two categories: those with a crater-like (eruptive) appearance, which lack a complete fibrous cap and are sometimes accompanied by thrombus adhesion, and those with a non-eruptive morphology, typically covered by an intact fibrous cap. The natural course of calcified nodules and the impact of different treatment strategies on clinical outcomes remain unclear.

The IVI CN China Registry is a prospective, observational, multicenter, single-arm registry study. Patients scheduled for PCI in the catheterization laboratory will undergo intravascular imaging based on the operator's clinical judgment, following standard medical practice. If calcified nodules are detected via intravascular imaging, patients will be further approached for informed consent to participate in the registry. The study plans to enroll 500 patients with coronary calcified nodules evaluated by intravascular imaging. Enrolled patients will be followed for up to 2 years.

1.2 Risks and Benefits to Study Subjects

As an observational registry study, no additional interventions are performed beyond standard care. The risks associated with this registry are expected to be consistent with those of routine intravascular imaging and coronary interventional procedures. Similar to all patients undergoing intravascular imaging and percutaneous coronary intervention (PCI), subjects in this study may experience adverse events and/or outcomes. These are described in the instructions for use of the devices employed and may include, but are not limited to:

- Acute stent thrombosis
- Allergic reactions to anticoagulants and/or antiplatelet agents, contrast media, or stent materials
- Angina pectoris
- Arrhythmias, including ventricular fibrillation, ventricular tachycardia, and heart block
- Arteriovenous fistula
- Cardiac arrest
- Cardiogenic shock/pulmonary edema
- Death
- Device entrapment requiring surgical intervention
- Embolism (air, tissue, thrombus, or device-related); including stent embolism or displacement
- Heart failure
- Bleeding events potentially requiring transfusion; including hemorrhage and hematoma (at access site)
- Hypertension or hypotension
- Local or systemic infection; including fever and pyrogenic reactions
- (Acute) myocardial ischemia or infarction
- Chest pain or pain at the access site
- Pericardial effusion or cardiac tamponade

- Renal insufficiency or failure
- Respiratory failure
- In-stent restenosis or aneurysm
- Stent deformation, collapse, or fracture
- Stent and vessel thrombosis/(vascular) occlusion
- Stroke/cerebrovascular accident/transient ischemic attack
- Total coronary occlusion
- Vascular injury requiring surgical repair or re-intervention; including coronary, femoral, or radial artery spasm, dissection, occlusion, perforation, rupture, or (pseudo)aneurysm

The potential benefits of this registry are no different from those of standard treatment. Based on the study findings, future patients undergoing imaging evaluation and PCI guidance for calcified nodules may benefit.

2. Study Objectives

To observe the natural course of calcified nodules evaluated by imaging and the clinical outcomes of different treatment strategies over a 2-year period.

2.1 Study Hypotheses

As an observational, prospective study, this registry will describe observed outcomes without pre-specified hypotheses.

3. Study Design

The CN-IVI Registry is a prospective, observational, multicenter, single-arm registry study planning to enroll 500 patients with calcified nodules evaluated by intravascular imaging.

After coronary angiography, patients will be screened according to the inclusion/exclusion criteria. Informed consent will be obtained. Participants will be followed for at least 2 years, with clinical visits at 6 months, 1 year, and 2 years to assess all clinical endpoints, including death, myocardial infarction, repeat revascularization, stent thrombosis, and stroke. Subjects are encouraged to complete all planned telephone and clinical visits.

The primary endpoint, Target Vessel Failure (TVF), is defined as the composite of cardiac death, target vessel myocardial infarction, or clinically indicated target vessel revascularization at 1 year. Definitions of the primary and secondary endpoints are detailed in Section 6.

The total study duration, from the first patient enrolled to the last patient completing follow-up, is expected to be approximately 4 years. If sufficient funding is available, the sponsor and executive committee may extend follow-up for all subjects to 5 years.

All deaths and major cardiovascular events, including components of the primary and secondary endpoints, will be adjudicated by an independent Clinical Events Committee (CEC) using standardized definitions. Details are provided in the CEC charter.

The CN-IVI Registry will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), ISO 14155:2020, requirements of the Ethics Committee, and Chinese regulations.

Note:

- Terminology is aligned with international clinical and regulatory standards.
- Complex medical concepts (e.g., calcified nodule morphology, endpoint definitions) are accurately translated while maintaining clarity.
- Risks and benefits are presented neutrally and objectively, as required for ethical clinical documentation.
- Study design details (e.g., follow-up schedule, endpoint adjudication) are explicitly stated to ensure transparency.

Flowchart: Patient Enrollment and Treatment Decision Process

1. **Coronary Angiography (CAG)**
    - The operator determines the necessity of intravascular imaging (IVI) based on clinical assessment.
    - Patient and family consent is obtained for IVI procedure.
2. **IVI Examination**
    - IVI identifies at least one calcified nodule lesion.
3. **Informed Consent for Registry Enrollment**
    - Informed consent is obtained for participation in the registry study.
4. **Treatment Decision**
    - The decision to intervene on the calcified nodule lesion and the selection of treatment strategy are **solely at the operator's discretion**.

Note: This flowchart outlines the sequential process from initial diagnostic imaging to enrollment and treatment decisions, emphasizing the operator's clinical judgment throughout.

Study Population

Patients presenting with asymptomatic myocardial ischemia, stable angina, unstable angina, or recent non-ST-segment elevation acute coronary syndrome (NSTE-ACS) with complex lesion characteristics.

Approximately 50 interventional centers across China

Calcified nodules evaluated by intravascular imaging (IVI), with or without interventional treatment

Enrollment period: 18 months

Primary Endpoint
TVF (Target Vessel Failure) defined as the composite of cardiac death, target vessel myocardial infarction (according to the Fourth Universal Definition of Myocardial Infarction), or clinically indicated target vessel revascularization.

3.2 Number of Study Centers
Approximately 50 research centers in China.

3.3 Sample Size
The study plans to enroll approximately 500 subjects.

3.4 Study Timeline

3.4.1 First Study Report
The initial report of the primary study results is scheduled after the last subject completes the one-year follow-up.

3.4.2 Subject Study Period
The enrollment period is expected to be approximately 18 months. All subjects will be followed for 2 years after enrollment. The total study duration is estimated to be approximately 48 months from the enrollment of the first subject.

All subjects will be followed from enrollment until the End of Research (EoR), which is anticipated to occur 2 years after enrollment.

3.4.3 Extended Follow-Up to 5 Years

All study subjects are scheduled for telephone or site visits at 2 years after enrollment. If sufficient research funding is available, the sponsor and steering committee may decide to extend telephone or clinical follow-up to 5 years after enrollment.

If follow-up is extended to 5 years, telephone or site visits will be arranged annually to collect information until the study concludes.

After obtaining initial informed consent, permission for 5-year clinical follow-up must be obtained via telephone contact. Clinical follow-up information will be collected from cardiologists, general practitioners, or public databases.

3.4.4 Study Closure

The study will be considered complete after the last follow-up of the last subject at all participating centers. The final study report will include all events and results from enrollment until the End of Research (EOR). If follow-up is extended to 5 years, interim reports with outcomes at 3, 4, and 5 years may be generated.

4. Study Population

This study plans to enroll 500 subjects who meet all inclusion criteria and none of the exclusion criteria.

4.1 Inclusion Criteria

Patients must meet the following criteria to be included:

1. Patients must be ≥18 years of age.
2. At least one calcified nodule lesion identified by coronary intravascular imaging.
3. Patients are willing and able to comply with study procedures and follow-up until the study concludes.
4. Subjects confirm understanding of the study risks, benefits, and alternative treatment options, and provide signed informed consent approved by the Ethics Committee before any protocol-related procedures.

4.2 Exclusion Criteria

Subjects unable to comply with follow-up, or whom the investigator deems unsuitable for participation for justified reasons.

5. Study Procedures

The study data collection schedule is detailed in Section 4.

5.1 Informed Consent and Subsequent Screening

After the investigator or designee reviews routine examinations and determines the patient's eligibility, the patient shall be informed about the study and asked if they are willing to participate. Protocol-specific procedures or changes to the subject's treatment must not begin until signed informed consent is obtained. After consent is provided, the patient receives a screening ID. The investigator or trained designee will explain the nature, scope, potential

risks/benefits of participation, and answer the subject's questions. Patients must be informed that they may decline further clinical follow-up for any reason without affecting their medical care or suffering any disadvantage.

All subjects (or legally authorized representatives) and investigators must sign and date the Ethics Committee-approved informed consent form before any protocol-specific procedures. Patients who cannot undergo proper informed consent procedures or follow-up activities (as judged by the investigator) or for whom signed consent cannot be obtained are ineligible for the registry.

Obtainment of consent, provision of a copy to the subject, and the date are recorded in the subject's medical records. The signed consent form is stored in the subject's medical record or site file, with a copy provided to the subject or representative. All subjects are consented using Ethics Committee-approved forms per local requirements. Pre-intervention angiographic results must confirm eligibility.

The informed consent form will also include the possibility of 5-year follow-up via telephone or clinical visits. Extended follow-up to 5 years is contingent on funding and at the discretion of the sponsor and funder.

5.1.1 Informed Consent in "Provisional" Revascularization

If a subject requires "provisional" revascularization (e.g., in NSTE-ACS), a staged informed consent process (in two parts) must be followed. First, an investigator orally informs the subject about the study, witnessed by independent catheterization lab personnel. Eligibility must be confirmed before information is provided. Oral consent is obtained, and the independent witness must sign the consent form before study procedures begin.

Within 24 hours post-procedure, the subject is fully informed via the complete patient informed consent process described in Section 5.1. The patient and investigator or designee must sign the full consent form.

The signed consent form is stored in the subject's medical record or site file, with a copy provided to the subject or representative. Obtainment of consent, provision of a copy, and the date are recorded in the medical record. Delays in obtaining full consent due to critical conditions (e.g., intubation) must be documented in the ICF.

5.2 Enrollment

All enrolled patients will be assigned a study ID. At enrollment, eligible lesion types will be recorded, including intravascular imaging data. If intervention is performed, procedural details will be collected.

5.3 Baseline Assessments

All subjects will undergo the following assessments before enrollment:

- Medical and cardiac history
- Cardiac-related medications

- Demographics and vital signs: age, gender, weight, height, blood pressure, heart rate, body temperature, and respiratory rate within 72 hours before angiography
- High bleeding risk assessment (ARC HBR)
- 12-lead ECG within 24 hours post-angiography (or within 72 hours for clinically stable patients). Date, time, and interpretation will be recorded in the EDC.
- Left ventricular ejection fraction and valvular disease status, if available from the past 90 days (e.g., CT, ultrasound, MRI, ventriculography) or during hospitalization
- Angina status assessed within 7 days before PCI
- Serious adverse events
- Pre-PCI laboratory results:
    - Local lab results within 28 days before PCI for white blood cells, platelets, hemoglobin, hematocrit, and serum creatinine
    - Local cardiac biomarker results (including CK-MB and troponin, per institutional standards, e.g., cTnI, cTnT, high-sensitivity or standard). For stable patients, collect within 72 hours before IVI-guided PCI; for unstable patients, within 24 hours. If biomarkers are elevated pre-PCI and a second measurement is taken, collect both. If timed data are unavailable, collect the most recent values. Prioritize troponin; collect CK-MB if available during clinical procedures.
    - Use the same biomarker assay for each blood draw per patient.
    - All biomarkers (e.g., CK-MB, hs-troponin, standard troponin) are acceptable; use consistent assays per patient.
    - The EDC will record the URL or ULN used by each center. If testing is done externally, request biomarker information from the referral center.

5.4 Calcium and Calcified Nodule Assessment

Severe calcification is identified by:

- Calcification arc >270 degrees
- Calcification arc without multiple reflection artifacts
- Presence of calcified nodules
- Location of calcified nodules, nodule type, presence of intact fibrous coverage, and thrombus attachment

5.5 Considerations for Interventional Management

1. Define landing zones
2. Avoid stent overlap at side branch bifurcations >2.5 mm
3. Stent selection criteria:
   a. Plaque burden <30% at 3 mm proximal and distal to the stent
   b. No large lipid pool
   c. Plaque burden <50%
   d. Proximal anchor zone at least 5 mm proximal to side branch bifurcations >2.5 mm to facilitate proximal optimization (POT)

1. **Final Stent Segment Criteria:**

- Minimum stent area (MSA) >5 mm² **or** MSA >90% of the distal reference lumen area.
- Plaque burden <50% within 5 mm proximal or distal to the stent edge.
- No edge dissection extending into the media with length >3 mm.

Procedural Considerations:

1. Missed lesions during pullback screening must be documented.
2. The following items should be considered when evaluating stent implantation results:
    - **Stent diameter:** Sized based on distal reference lumen area or external elastic membrane (EEM) area. If significant tapering exists, use proximal upsizing with post-dilation balloons.
3. Reasons for suboptimal results must be recorded in the eCRF.

Optimal Stent Implantation Criteria:
a. If edge dissection >3 mm is detected, add an additional stent.
b. For non-left main (LM) lesions with MSA <5 mm² or MSA <90% of distal reference lumen area, perform additional high-pressure non-compliant (NC) balloon post-dilation.
c. For LM lesions:

- Final stent area must target ≥8 mm² for the LM trunk,
- ≥7 mm² for the LM bifurcation (point of convergence, POC),
- ≥6 mm² for the LAD,
- ≥5 mm² for the LCX (per Kang et al. criteria).
  d. If plaque burden exceeds 50% at the edges, add an additional stent.

5.4.2.2 Treatment Recommendations by Lesion Type

- IVI evaluation is strongly recommended both pre- and post-PCI to guide treatment strategy.
- **Bifurcation lesions:**
    - Both single-stent and two-stent strategies are permitted. Final kissing balloon and proximal optimization (POT) are generally recommended. Post-PCI IVI for both branches is encouraged if technically feasible.
- **Left main (LM) lesions:**
    - Pre-PCI IVUS is strongly recommended. Stent technique depends on lesion location. For true bifurcation LM stenosis, DK-crush technique is suggested. If a two-stent technique is used, post-PCI IVI for both branches is advised.
- **In-stent restenosis (ISR):**
    - Pre-PCI IVI is strongly recommended to assess the mechanism of restenosis.
- **Long lesions (estimated stent length >28 mm):**
    - Pre-PCI IVI is strongly recommended to evaluate lesion length and stent sizing.
- **Chronic total occlusion (CTO):**

- Patients with CTOs can only be enrolled after successful recanalization. Failure to advance the coronary guidewire into the true distal lumen of the chronic occlusion renders the patient ineligible.

5.4.2.3 Post-Procedural IVI

Post-procedural IVI is mandatory. All stent segments must be evaluated by IVI before concluding the procedure (refer to Section 5.4.2.1).

5.5 Supplementary Recommendations

- IVI must be used to treat all lesions (complex and non-complex) during the initial or staged procedure. Vessels with diameter <2.5 mm do not require IVI.
- Subjects should undergo optimal revascularization per investigator judgment, which may imply incomplete revascularization.
- For "borderline or intermediate non-complex lesions" (50-70% diameter stenosis by visual estimation), coronary physiology testing is recommended to confirm lesion significance before treatment. Lesions not severe by angiography, IVI, or physiology should not undergo PCI.
- For non-complex lesions, pre- and post-treatment IVI-guided assessment is required to optimize lumen dimensions (except for distal lesions, tortuous vessels, or proximal lesions in large vessels).
- Lesion preparation with balloons or approved devices is at the operator's discretion to facilitate stent delivery and expansion.
- Only commercially available second-generation drug-eluting stents (DES) may be used.
- Non-compliant balloon post-dilation (≥18 atm) within all stent edges is recommended to optimize lumen results.
- IVI criteria for optimal PCI are defined in Section 5.4.2.1.
- For diffuse disease or tandem lesions, use a single long stent rather than two shorter side-by-side or overlapping stents. Staged procedures are allowed, especially for complex multivessel disease or subjects receiving high radiation/contrast during the initial procedure.

5.6 Staged Procedures

Given the complexity of enrolled subjects, staged procedures may be necessary. Decisions are based on patient factors (e.g., renal function, contrast exposure, fatigue), lesion complexity (e.g., calcification), prolonged procedures, complications, or instability. In the CN-IVI study, staged procedures must meet:

1. Intent documented in EDC within 30 days of the first procedure (or 48 hours before the staged procedure);
2. Lesions to be treated must be pre-defined in EDC and not involve the index vessel (except CTOs);
3. Procedure must occur within 45 days of initial PCI (90 days for CTOs);
4. Symptoms must be stable between procedures (acute ischemia precludes staging). For CTOs, successful recanalization is required for enrollment. Failure to advance the guidewire into the true distal lumen renders the patient ineligible.

After CTO recanalization, delayed treatment may be needed due to diffuse atherosclerosis/negative remodeling. Staged procedures for CTOs may be planned within 45-90 days.
Per CTO-ARC consensus, modifications, staged secondary procedures, and staged optimizations must be clearly documented and not considered ad hoc procedures.
The Clinical Events Committee (CEC) will determine whether a second procedure qualifies as staged (included in initial treatment) or revascularization (counted as an endpoint).
Second-generation DES should be used in staged procedures. Assessments mirror baseline procedures. Staged procedures do not alter follow-up schedules.

5.7 Medication Therapy

5.7.1 Pre-PCI

- Dual antiplatelet therapy (DAPT) must be initiated pre-PCI.
- **Aspirin:** Pre-treated per local guidelines.
- **ADP antagonists (e.g., clopidogrel, prasugrel, ticagrelor):** Pre-treated per local guidelines.
- **Other medications:** Statins, beta-blockers, ACE inhibitors, unfractionated heparin, etc., are at the physician's discretion.

5.7.2 Intraprocedural Pharmacology

- **Unfractionated heparin or low molecular weight heparin:** Used per local guidelines.
- **GP IIb/IIIa inhibitors:** Not encouraged in subjects adequately pre-treated with ADP antagonists. Use at operator's discretion per local guidelines.

5.7.3 Post-PCI

- **Antiplatelet therapy:** ADP antagonists should be used per local guidelines, considering clinical presentation, ACS/stable CAD, bleeding risk, anticoagulant use, or coagulation disorders.
- **Aspirin:** Used with DAPT per local guidelines.
- **(N)OAC for subjects with indications:** Managed per latest local guidelines.

5.8 Post-PCI Blood Sample Collection

- Cardiac biomarkers must be collected within 24 hours post-PCI. Serial measurements are recommended if biomarkers are elevated until a decline is observed (not mandatory if not per local practice).

5.9 Discharge

Assessments at discharge:

- Angina status

- ECG within 24 hours post-procedure or before discharge (date, time, and interpretation recorded in EDC)
- Serious adverse events
- Cardiovascular medications
  Subjects must be informed about required DAPT and follow-up schedule.

5.10 6 Months Post-Enrollment (±30 days): Telephone or Site Visit
Assessments:

- Angina grade
- Cardiac-related medications
- Serious adverse events

5.11 1 Year Post-Enrollment (±30 days): Telephone or Site Visit
Assessments:

- Angina grade
- Cardiac-related medications
- Serious adverse events

5.12 2 Years Post-Enrollment (±30 days): Telephone or Site Visit
Assessments:

- Angina grade
- Cardiac-related medications
- Serious adverse events
- If study extension is not planned, inform subjects of study conclusion after the 2-year visit (per Section 5.15).

5.13 Additional Annual Follow-Up (±30 days): Telephone Visit
Planned follow-up concludes at 2 years. However, with sufficient funding and sponsor/executive committee decision, annual follow-up may continue for years 3, 4, and 5 via telephone visits assessing:

- Angina grade
- Cardiac-related medications
- Serious adverse events

5.14 Image Transmission and Feedback to Study Centers
Angiographic images will be transmitted in DICOM format via AGMedNet to the IVI and Angiography Core Laboratory (Cardialysis, Rotterdam, The Netherlands). DICOM files must not contain patient names or birth dates; materials must be labeled with the enrollment ID (i.e., anonymized data). Post-PCI images for all subjects will be reviewed by the independent IVI Core Laboratory and evaluated against optimization standards. Feedback will be provided to the

clinical trial center when necessary. To ensure timely review, DICOM materials must be transmitted to Cardialysis via AGMedNet within 4 weeks post-procedure.

5.15 Missed Visits
Every effort should be made to ensure subjects adhere to site and telephone visits. If a subject cannot complete a visit, the investigator or designee must document the reason and attempt to obtain additional information from the subject.

5.16 Loss to Follow-Up
Subjects will not be considered "lost to follow-up" until the 2-year follow-up period ends. Loss to follow-up is defined as failure to complete the final assessment despite multiple contact attempts. At each site visit time point, at least three attempts must be made to contact the subject. Available clinical data or vital signs should continue to be collected from interventional centers, referral hospitals, or general practitioners. All contact attempts must be documented, and an end-of-study form completed. Subjects lost to follow-up will not be replaced.

5.17 Withdrawal
Study visits and data collection continue for all enrolled subjects until the last visit. Subjects who explicitly refuse further clinical follow-up and data collection are considered "withdrawn." Participants may decline further follow-up for any reason without affecting their medical care or suffering disadvantage.
If a subject withdraws consent for continued data collection, data collected prior to withdrawal will be evaluated. While subjects are not obligated to provide a reason, the investigator should respectfully attempt to determine the cause. The reason for withdrawal should be documented if possible, and an end-of-study form completed.
After withdrawal, subject-specific data (e.g., image readings, blood sample analyses) generated from materials obtained before withdrawal may be retained and included in statistical analyses per the statistical analysis plan. Subjects have the right to object to the generation and processing of post-withdrawal data.
High withdrawal or loss-to-follow-up rates may compromise study interpretability. Therefore, unnecessary withdrawals should be avoided. If a subject withdraws, every effort should be made to collect any data within the scope of their consent. Observations should be completed and reported as fully as possible.
Withdrawn subjects will not be replaced.

5.18 End of Research (EoR) Definition
All subjects will undergo a final telephone visit at 2 years (±30 days) post-enrollment. The study may be extended to include additional annual telephone follow-ups up to 5 years, contingent on funding and sponsor/executive committee decision. Subjects lost to follow-up at 2 years will be considered permanently lost. Study completion is defined as the date of the last visit for the last subject across all trial sites. The final study report will include all outcomes between enrollment and EoR. If follow-up is extended to 5 years, interim reports with outcomes at 3, 4, and 5 years may be provided.

6. Study Endpoints
Time-to-first-event analysis will be primarily used for clinical endpoints.

Primary Endpoint:
TVF (Target Vessel Failure) is defined as the composite of cardiac death, target vessel myocardial infarction*, or clinically indicated target vessel revascularization.
*Periprocedural myocardial infarction will be defined according to ARC-2 but is excluded from the primary composite endpoint. Spontaneous myocardial infarctions (>48 hours post-procedure) will be classified according to the Fourth Universal Definition of Myocardial Infarction.

Key Secondary Endpoints:

1. Composite of target vessel myocardial infarction* and clinically indicated target vessel revascularization.
2. Clinically indicated target vessel revascularization.
3. Composite of cardiac death and target vessel myocardial infarction*.
4. Target lesion failure, defined as the composite of cardiac death, target vessel myocardial infarction*, or clinically indicated target lesion revascularization.
5. Target lesion revascularization.
6. Cardiac death.

Other Clinical Endpoints:

1. Patient-oriented Composite Endpoint (PoCE): Defined as all-cause death, stroke, myocardial infarction*, and any revascularization.
2. Device-oriented Composite Endpoint (DoCE): Defined as cardiovascular death, target vessel myocardial infarction*, and clinically indicated target lesion revascularization.
3. Target vessel revascularization.
4. Stroke.
5. Definite and probable stent thrombosis.
6. Periprocedural myocardial infarction.
   *Periprocedural myocardial infarction will be defined according to ARC-2 but is excluded from the composite endpoint. Spontaneous myocardial infarctions (>48 hours post-procedure) will be classified according to the Fourth Universal Definition of Myocardial Infarction.

Procedure-Related Endpoints:

1. Procedure duration.
2. Total contrast agent volume used.
3. Device utilization.

Other Procedural Safety Endpoints:

1. Acute kidney injury.
2. Vascular access site complications.
3. Bleeding events.

4. Major intraprocedural complications, including Type C-F dissection, perforation, persistent slow-flow/no-reflow, acute lumen closure, distal embolization, thrombosis, and major side branch occlusion (lumen diameter ≥2 mm).
5. Perforation events according to the Ellis criteria.

Core Laboratory Report:

1. Achievement of optimal IVI criteria.

7. Statistical Methods

7.1 Demographic Analysis

Analyses will be performed according to the intention-to-treat (ITT) principle, including all enrolled subjects. This group constitutes the Full Analysis Set (FAS) as defined in ICH E9 guidelines. Per-protocol and as-treated population analyses will serve as sensitivity analyses.

7.2 Primary Endpoint Analysis

The primary endpoint will be analyzed using time-to-first-event analysis based on the ITT principle, including all adjudicated primary endpoints occurring from enrollment through the 1-year follow-up.

Follow-up time for each subject begins on the enrollment date and should be as long and complete as possible. In time-to-event analysis, follow-up is censored on the day the observation ends: at 1 year, on the date of non-cardiac death, or on the last date adequate data were obtained, whichever comes first. Endpoints occurring after the 1-year follow-up, not included in the initial primary results publication, will be reported in the final study report.

Kaplan-Meier estimates and cumulative risk curves will be used to assess the timing of endpoint events. Cause-specific hazard ratios and 95% confidence intervals will be generated using Cox proportional hazards models. Censoring occurs at the time of competing risk events (non-cardiac death) or at 1-year follow-up (as defined above). Further details are provided in the statistical analysis plan (SAP). For subjects experiencing an endpoint event, the time-to-event is calculated as the difference between the event date and the enrollment date defined in the SAP. For subjects without an event, censoring time is calculated as the difference between the end-of-observation date (as defined above) and the enrollment date. The frequency of endpoint events will be presented as percentages and incidence per 100 patient-years.

The primary endpoint analysis will also include pooled results from the 1-year data. A propensity-matched analysis comparing Eruptive CN patients with Non eruptive CN is anticipated.

7.3 Secondary Endpoint Analysis

Secondary endpoints will be analyzed similarly to the primary endpoint, using Kaplan-Meier methods and Cox proportional hazards regression. For secondary endpoints excluding cardiac death, all-cause death will be analyzed as a competing risk. Formal hypothesis testing will not be performed.

7.4 Other Clinical Endpoint Analysis

Other clinical endpoints will be analyzed similarly to primary and secondary endpoints using

Kaplan-Meier methods and Cox proportional hazards regression, without formal hypothesis testing. Procedural outcomes will be reported as binary or continuous variables using standard tests. Further details on statistical methods, including handling of missing data, are provided in the SAP.

7.5 Sample Size Determination

The sample size is set at 500 enrolled subjects, with a maximum of 125 subjects (25%) per center.

7.6 Pre-Planned Subgroup Analyses for the Primary Endpoint

- By whether calcified nodule ablation therapy was performed (rotational atherectomy / orbital atherectomy)
- By clinical presentation (ACS vs. non-ACS)
- By chronic kidney disease status (yes/no)
- By diabetes status (yes/no)
- By lesion type: chronic total occlusion (yes/no)
- By post-PCI functional assessment based on IVI (threshold analysis)

8. Safety Assessment and Reporting

8.1. Safety Information Reference

The anticipated device adverse reactions for the IVI catheters and stents used in this study are described in the Instructions for Use (IFU), with some detailed in IFU Section 1.5. For reference, the list of anticipated device adverse reactions is provided in Section 1.5. If updates to the applicable IFU during the registry study have significant implications, Section 1.5 may be revised accordingly.

8.2. Safety Reporting

The principal investigator at each participating study center is responsible for ensuring all staff involved in the study are familiar with this section.

8.2.1. Definition of Adverse Event (AE) (Reference: *Good Clinical Practice for Medical Device Clinical Trials [2022] Order No. 28*)
A medical device adverse event refers to any adverse medical event occurring during the clinical trial of a medical device, regardless of its relationship to the investigational device.

The CN-IVI Registry adopts a similar definition from ISO 14155:2020:
An AE is defined as any untoward medical occurrence, unintended disease or injury, or unintended clinical sign (including abnormal laboratory findings) in a subject, user, or other person, whether or not related to the investigational device.

Note: This definition includes both expected and unexpected events. It also covers events related to the investigational device or associated procedures.

8.2.2. Definition of Serious Adverse Event (SAE) (Reference: *Good Clinical Practice for Medical Device Clinical Trials [2022] Order No. 28*)
Refers to any event occurring during the clinical trial that results in death or serious deterioration in health, including:

- Fatal illness or injury;
- Permanent impairment of body structure or function;
- Necessitating hospitalization or prolongation of hospitalization;
- Requiring medical or surgical intervention to prevent permanent impairment of body structure or function;
- Events leading to fetal distress, fetal death, congenital anomalies, or birth defects.

The CN-IVI Registry adopts a similar definition from ISO 14155:2020:
An adverse event is classified as "serious" if it results in any of the following:

- Death;
- Serious deterioration in the subject's health, resulting in:
    - Life-threatening illness or injury;
    - Permanent impairment of body structure or function, including chronic disease;
    - Necessitating hospitalization or prolongation of existing hospitalization;

- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment of body structure or function.

8.2.3. Definition of Device Deficiency (Reference: *Good Clinical Practice for Medical Device Clinical Trials [2022] Order No. 28*)
Device deficiency refers to any unreasonable risk that may endanger human health or safety during normal use of the medical device in the clinical trial, such as labeling errors, quality issues, or malfunctions.

CN-IVI Registry uses a more detailed definition from ISO 14155:2020:

Device Deficiencies and Malfunctions
If the investigator identifies a device malfunction that has caused or could cause death or serious harm to the subject, user, or others, or receives a complaint regarding a device deficiency, the investigator must report the malfunction or complaint to the device manufacturer within 24 hours of discovery and provide a copy of the report to the sponsor. The sponsor is responsible for taking necessary actions in response to the device malfunction to protect study subject safety, such as temporarily suspending the study.

A device deficiency is defined as any inadequacy in the characteristics, quality, durability, reliability, safety, or performance of the investigational device, including malfunctions, use errors, or insufficient information provided by the manufacturer.

Where possible, the study site should return the malfunctioning device to the manufacturer for inspection. The device manufacturer is responsible for handling all complaints, deficiencies, and reported device malfunctions related to medical device quality, including any actions deemed necessary, such as reporting events to regulatory authorities and initiating recalls. The device company and participating clinical trial sites will discuss such malfunctions or complaints. Further details are provided in the safety reporting plan.

8.2.4. Definition of Unanticipated Adverse Device Effect (21 CFR Part 812)
A serious adverse effect on health or safety, or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or incidence in the investigational plan or application (including supplementary plans or applications), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

8.2.5. Definition of Unanticipated Serious Adverse Device Event (USADE) (ISO 14155:2011, MEDDEV 2.7/3 rev 5/2015)
A serious adverse device effect whose nature, incidence, severity, or outcome has not been identified in the risk analysis.

Note: An anticipated serious adverse device event (ASADE) refers to an effect whose nature, incidence, severity, or outcome has been identified in the product specifications.

Underlying diseases are not reported as AEs unless their severity or frequency increases during the study. Deaths are not reported as AEs but are reflected as outcomes of specific SAEs.

All AEs occurring after subject enrollment, whether during or after the procedure, must be recorded in the EDC. If an AE is caused by a device deficiency or other device-related issue, it must be reported in the Electronic Data Capture (EDC) system.

Hospitalization is defined as the admission of a subject, with the following exceptions:

- Hospitalization for uncomplicated elective/planned procedures (i.e., planned prior to enrollment) is not reported as an SAE.
- If a complication or AE occurs during an elective/planned hospitalization (i.e., planned prior to enrollment) and meets the definition outlined in the protocol, the complication or AE must be reported as an AE or SAE. The initial elective/planned hospitalization itself is not reported as an SAE.

8.2.6. Recording of Adverse Events or Serious Adverse Events

In accordance with the *Good Clinical Practice for Medical Device Clinical Trials [2022] Order No. 28* of China, for serious adverse events, the investigator must immediately provide appropriate treatment to the subject. Simultaneously, the investigator must report to the sponsor, the medical device clinical trial institution management department, and the ethics committee within 24 hours of discovery or notification. Follow-up should be conducted as per Chinese GCP and the clinical trial protocol (details in Section 8.2.7), and a follow-up report on the serious adverse event must be submitted.

The sponsor must, within 7 days of learning of a death or life-threatening serious adverse event related to the trial medical device, and within 15 days of learning of a non-death or non-life-threatening serious adverse event related to the trial medical device or other serious safety risk information, report to other participating medical device clinical trial institutions, ethics committees, and principal investigators. The sponsor must also report to the drug regulatory department of the province, autonomous region, or municipality directly under the central government where the sponsor is located, and to the drug regulatory department and health administration department of the province, autonomous region, or municipality directly under the central government where the medical device clinical trial institution is located. Risk control measures must be implemented.

If widespread serious adverse events related to the trial medical device or other major safety issues occur, the sponsor must suspend or terminate the medical device clinical trial. Reports must be made to the management departments of all medical device clinical trial institutions, ethics committees, and principal investigators, to the drug regulatory department of the province, autonomous region, or municipality directly under the central government where the sponsor is located, and to the drug regulatory departments and health administration departments of the provinces, autonomous regions, or municipalities directly under the central government where all medical device clinical trial institutions are located.

8.2.7. Safety Reporting Procedures

During the study, investigators will monitor each participant for the occurrence of AEs (SAEs). For this protocol, reporting of AEs (SAEs) begins from the formal enrollment of the subject and continues through the last follow-up visit. All intraprocedural AEs (SAEs) must also be reported. If an event meets SAE criteria, it should be reported within 24 hours as stipulated in Section 8.2.6 without undue delay. It is highly recommended that all SAEs for a single patient be entered into the EDC system within a 30-calendar-day window. Only EDC data will be used for outcome reporting and endpoint adjudication and will be cross-checked with investigator-reported SAEs. When reporting events in the EDC system, it is not necessary to send supporting source documents for the events. For clinical event adjudication and safety verification, Cardialysis will request supporting source documents for events. All SAEs will be followed until the event is resolved (with or without sequelae).

The sponsor is responsible for classifying SAEs according to local standard practices and for the ongoing safety assessment of the clinical study. The sponsor should review the investigator's assessment of all SAEs and device deficiencies, determine and document in writing the sponsor's judgment on severity and relationship to the investigational device. If there is a discrepancy between the sponsor's and the principal investigator's opinions, both opinions should be reflected.

All devices used in this study protocol have been approved by the regulatory authorities in the region where the study is conducted and are used within the approved indications.

Details on SAE handling, distribution, and reporting are provided in the Safety Reporting Plan.

8.3. Risk Analysis

Risk-benefit assessment is detailed in Section 1.5, and ongoing risk-benefit assessment is covered in Section 9.7.1.5.

9. Data Integrity and Quality Assurance

9.1. Regulatory Statement

The protocol, ICF, and other study-related documents will be submitted to the EC and any other regulatory authorities as required by local regulations. The study will be conducted in accordance with the ethical principles of ISO 14155:2020 "Clinical investigation of medical devices for human subjects—Good Clinical Practice," the relevant sections of the ICH GCP guidelines, the "Medical Device Clinical Trial Quality Management (No. 28 [2022])," and the Declaration of Helsinki. This study may only commence after obtaining the necessary approval/favorable opinion from the EC and/or regulatory authorities. The study must comply with all additional requirements from the EC or regulatory authorities.

9.2. Data Collection System

The data recording tool for this study is a validated EDC system.

To protect the data within the EDC system, all access is password-protected. All relevant study personnel (Sponsor, Investigational Site, Contract Research Organization (CRO), or others) seeking access to the EDC system will receive training before access is granted. The Investigator must maintain a signature and delegation log signed by qualified and trained site staff. All site personnel authorized to enter and/or correct data in the EDC system are listed in the signature and delegation log.

All personnel with access to the EDC system are supported by a help desk. The EDC system includes a system-generated audit trail that records any changes made to data fields, including who made the change, the reason for the change, and the date and time of the change.

9.2.1 EDC Entry

It is highly recommended that all data entry into the EDC system be completed within 30 calendar days after subject enrollment/visit/contact, including all reported SAEs, to allow monitors to review subject status throughout the enrollment period (see Section 9.5). Subject data in the EDC system is entered by the Investigator or a qualified designee and is reviewed and signed (electronically) by the Investigator. Data entered into the EDC system is supported by source documents maintained by the investigational site for all subjects enrolled in the study (see Section 9.3).

Before the first subject is enrolled at a site, the site staff will be provided with EDC system data entry guidelines.

9.2.2 Recording Data for Screen Failures

A subject may have signed the ICF but is later considered a screen failure after subsequent screening procedures. This is referred to as a screen failure. Data from screen failures will not be recorded in the EDC system. Only formally enrolled patients will be recorded in the eCRF.

9.3. Study Documentation

Source documents are original records containing source data. Examples include original records or certified copies of hospital records, clinical and office charts, laboratory records, subject diaries, and records kept by laboratories involved in the clinical study. Source data can be either paper-based or electronic. All data intended for entry into the EDC system must have source documents available at the investigational site. All data intended for entry into the EDC system must have source documents accessible at the investigational site.

In accordance with the regulations described in Section 9.1, the Investigator and study staff are responsible for maintaining a comprehensive and centralized file of all essential study-related documents (the Investigator Site File) for inspection at any time by representatives of the Sponsor and/or applicable regulatory authorities. The Investigator and study staff must ensure that only authorized personnel, auditors, and monitors have access to the study data.

9.4. Data Management

Clinical data management will be performed according to applicable CRO standards and data cleaning procedures. This applies to data recorded in the EDC system as well as data from other (external) sources (e.g., review committees).

9.5. Quality Assurance

Each clinical investigational site will conduct internal quality management for the conduct of the study, data and biospecimen collection, documentation, and completion. Quality control procedures will be implemented, starting with EDC and data QC checks run on the database. Any missing data or data anomalies will be communicated to the investigational site for clarification/resolution. Furthermore, monitoring visits, and potentially audits and inspections, ensure oversight of the entire quality control process.

9.5.1 Audits and Inspections

To ensure compliance with the guidelines and regulations described in Section 9.1, members of the CRO's Quality Assurance department may schedule a site audit to assess the site's study performance and the performance of study documents originating from the site. The Investigator will be informed of the audit findings.

Additionally, inspections may be conducted by representatives of health regulatory authorities and the EC. The Investigator must notify the Sponsor immediately of any such inspection. Audits and inspections may occur at any time during or after the completion of the study.

9.5.2 Monitoring

According to the guidelines and regulations described in Section 9.1, the Monitor will contact the site before the study begins to review the protocol, study requirements, and the site staff's responsibilities for meeting regulatory, ethical, and Sponsor requirements.

Per the monitoring plan, on-site and/or remote monitoring visits will be conducted throughout the study to verify compliance with the protocol/amendments; validate the authenticity, completeness, accuracy, and consistency of the data; verify that the rights and well-being of human participants are protected; and confirm adherence to the guidelines and regulations described in Section 9.1. The CN-IVI Registry does not constitute an investigation of a marketed device but aims to describe the outcomes of this clinical strategy; The Monitor must have access to subjects' medical records and other study-related documents. If electronic patient records (ePD) are used, controlled read-only access must be arranged for the Monitor. If the ePD is not validated, or if the Monitor cannot access it, there must be a procedure for generating certified copies of source documents.

The Monitor will inform the Investigator of and document significant deviations from the protocol, SOPs, guidelines, and regulations as described in Section 9.1, and will verify that

appropriate measures are taken to prevent the recurrence of identified deviations. Further details are available in the monitoring plan.

9.6. Investigator Responsibilities

Before subject enrollment begins, the Site Principal Investigator must read and understand this study protocol and sign and date the protocol signature page. The Site Investigator Agreement documents all conditions agreeing to the study protocol and the agreement to conduct the study accordingly. The Site Principal Investigator is responsible for ensuring the study is conducted in accordance with the provisions in Section 9.1.

The Site Principal Investigator, site staff, and the site agree to permit the Monitor, Auditor, or Inspector direct access to all relevant source data/documents and will cooperate with the Monitor/Auditor/Inspector in discussing any findings.

9.7. Sponsor Responsibilities

9.7.1 Sponsor Role

The Sponsor is fully responsible for the conduct of the study, including ensuring the study complies with the international standards and regulatory requirements of the relevant (competent) authorities described in Section 9.1.

9.7.1.1. Overall Responsibilities

Before allowing subject enrollment to begin at a site, the Sponsor is responsible for selecting the Investigator, ensuring EC approval is obtained (if applicable), and executing a clinical trial agreement with the Investigator and/or the hospital. Furthermore, the Sponsor is responsible for ensuring adequate supervision of the clinical investigational site.

9.7.1.2. Selection of Clinical Investigators and Sites

The Sponsor will select qualified Investigators and sites with an adequate patient population to meet the study requirements.

9.7.1.3. Training of Investigators and Site Staff

Training of the Investigator and appropriate clinical site staff will be the responsibility of the Sponsor and may be conducted during investigator meetings, site initiation visits, and/or other appropriate training sessions. Training on IVI acquisition/use will be provided before the first subject is enrolled. The Investigator is responsible for training site staff who were not present during the initiation visit.

9.7.1.4. Documentation

The Sponsor will collect, store, safeguard, and ensure the completion of the following documents by the relevant parties:

- All study-related documents (e.g., protocol, EC approvals and opinions, notifications or approvals and opinions, patient information and informed consent forms, relevant correspondence, etc.)
- Signed and dated EDC pages
- Records of any SAEs reported to the Sponsor during the clinical study
- Any statistical analyses and underlying supporting data
- The final report and/or publications of the clinical study

9.7.1.5. Ongoing Risk-Benefit Analysis

The Sponsor is responsible for the continuous evaluation of the risk-benefit analysis throughout the study. An independent Data and Safety Monitoring Board has not been contracted for this study.

9.7.1.6. Other Sponsor Responsibilities

Other legal responsibilities of the Sponsor, including patient insurance, are described in Section 9.1.

9.7.2 Sponsor Delegation of Tasks

For this study, the Sponsor has delegated specific tasks to a Clinical Research Organization (CRO), as described in Section 12. Whenever "Sponsor" is mentioned in this protocol, it includes its delegate(s), where applicable.

9.8. Archiving

Upon study completion, essential documents will be archived in a manner that ensures they are readily available upon request by regulatory authorities. Subjects' medical records shall be retained for the maximum period permitted by applicable law and the investigational site. Essential clinical registry documents (including EDC), aside from subject medical records, must be retained for at least 10 years after registry completion or termination according to Chinese requirements, and for at least 15 years according to Dutch requirements. Study documents must not be destroyed without prior written consent from the Sponsor and the Investigator. If the Investigator wishes to transfer the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new custodian and/or the new location.

9.9. Study Termination or Temporary Halt and Premature Study Conclusion

The Sponsor will notify the relevant regulatory authorities of the study conclusion within 90 days. If the study is temporarily halted, the Sponsor will immediately notify the relevant regulatory authorities, including the reason for the halt. If the study is concluded prematurely, the Sponsor shall notify the relevant regulatory authorities within 15 days, including the reason for the premature termination. Within one year after the study conclusion, the Investigator/Sponsor

shall submit a final study report to the relevant regulatory authorities, which includes the study results or any publications/abstracts of the study.

This study may be temporarily suspended or terminated prematurely if fully justified and reasonable grounds exist. The party suspending or terminating will provide written notice to the Investigator, the funding party, and the regulatory authorities, documenting the reason for the suspension or termination. If the study is terminated prematurely or suspended, the Investigator shall immediately notify the EC and provide the reason for the termination or suspension. Study subjects will be contacted as appropriate and informed of changes to the site visit schedule.

The study may potentially resume once the issues are resolved and the suspending party is satisfied.

10. Ethical and Legal Aspects

10.1 Funding, Financial Disclosure, and Insurance

This study is sponsored by Zhongshan Hospital, Fudan University, as an investigator-initiated registry study. Boston Scientific International Medical Trading (Shanghai) Co., Ltd. has provided a grant to fund this study.

A clinical registry agreement will be executed between the Investigator and/or the institution and the Sponsor before subject recruitment.

As this is a post-market clinical registry study, the Sponsor is not required by local regulations to purchase insurance for the patients.

10.2 Ethical and Legal Conduct of the Study

The procedures set forth in this protocol related to the implementation, evaluation, and documentation of this study are designed to ensure that the Sponsor and Investigator adhere to the guidelines stipulated in Section 9.1. All aspects of the study's conduct require strict compliance with all quality standards set out in this protocol; the Investigator must not modify or change the procedures described herein.

No amendments to the study protocol may be made by the Sponsor or the Investigator without mutual agreement. However, the Investigator or Sponsor may deviate from or change the protocol to eliminate apparent immediate hazards to the study subjects without prior EC/Sponsor approval/favorable opinion. The implemented deviation or change, the reason for it, and, where appropriate, a proposed protocol amendment should be submitted to the EC/institution head/Sponsor as soon as possible.

10.3 Protocol Amendments

As the study progresses, any appropriate study protocol amendments will be communicated to the Investigator by the Sponsor. All substantial protocol amendments will undergo the same review and approval process as the original protocol. All substantial and non-substantial amendments are handled according to local regulations and may be submitted to the local competent authorities for notification or approval. Unless changes must be implemented immediately for subject safety reasons, they shall be implemented after the protocol amendment has received EC approval.

10.4 Patient Information and Informed Consent

The ICF and all other written information provided to subjects will be revised when important new information becomes available that might be relevant to the subject's consent, or when changes are required due to a protocol amendment affecting the subject information sheet and/or the content of the written ICF. The Investigator will promptly inform subjects about the changes and ask subjects to sign the revised ICF to confirm their participation in the study. Any revised written ICF and written information must receive EC approval/favorable opinion before use.

10.5 Confidentiality

All records that could identify subjects will be kept confidential to the extent permitted by applicable laws and/or regulations. Subject names will not be provided to the Sponsor. If a subject's name appears on any other document (e.g., angiograms, IVUS, ECG), it must be removed before a copy of the document is provided to the Sponsor. Images sent to the angiographic core laboratory are anonymized. Study results stored on computers will be stored in accordance with local data protection laws. If the study results are published, the identity of the participants will remain confidential. The Investigator will retain a list to allow identification of the subjects. A subject identification code list will be used to link data to the subjects, only insofar as it is necessary to be able to trace the data back to an individual subject (for 10 years in China). The code must not be based on patient initials and date of birth. The key to the code shall be kept by the Investigator. The processing of personal data will comply with the Chinese privacy regulations and the EU General Data Protection Regulation (GDPR), as well as national legislation.

11. Publication Policy

The Steering Committee is committed to publishing and widely disseminating the study results. The data from this study will not be withheld, regardless of the outcome. The CN-IVI Registry was initiated by Professor Junbo Ge and is scientifically driven by the Steering Committee, with ECRI acting as a co-organizer. All public presentations and the writing and submission of manuscripts are conducted under the leadership of the Steering Committee. This study represents the collaborative effort of the Steering Committee, Investigators, Professor Junbo Ge (Sponsor), and ECRI representatives. Therefore, the parties have agreed that suggestions from all parties

regarding manuscripts should be considered when preparing the final scientific documents for publication or presentation, according to the agreed publication policy.

The final locked database will be stored at the data management centers of the local CRO and Cardialysis. The CRO may not publicly release data or study-related materials, presentations, or manuscripts without the explicit written permission of the Sponsor. The final locked database will also be transferred in its entirety to Cardialysis. Cardialysis will be responsible for analyzing the combined dataset, including the results of the registry, and performing aggregated data analysis. Prior to the publication of the primary results, the Principal Investigator (PI) will have full access to the data (i.e., all requested results will be provided). After the publication of the primary results for the primary endpoint event, the PI, high-enrolling personnel, and the manufacturer may request secondary analyses under the auspices of the Steering Committee. Proposals must be submitted to the Sponsor, who will liaise with the Steering Committee and the Publications Committee to determine priority, relevance, scientific merit, and novelty. Approved subgroup analyses will be handled by the Cardialysis statistics department. The publication and/or presentation of results from individual centers is not permitted prior to the publication and/or presentation of the multi-center results. All data from individual centers intended for public dissemination must be generated from the central database—local database projects are not permitted. All proposed publications and reports originating from or related to the study (whether from multi-center or single-center analyses) must be submitted to Professor Junbo Ge. Mr. Ge is responsible for liaising with the Publications Committee for review and approval prior to submission for publication or presentation.

12. Study Organization

12.1 Sponsor

Zhongshan Hospital, Fudan University
Shanghai, China

12.2 Steering Committee

The Steering Committee is responsible for the overall design, implementation, and supervision of the study, including the development of any protocol amendments. The Steering Committee also periodically reviews the study's progress to ensure subject safety and study integrity. The composition of the Steering Committee and other details are outlined in the Steering Committee charter.

12.3 Data and Safety Monitoring Board (DSMB)

As the CN-IVI Registry is an observational study of commercial devices and treatment strategies in accordance with guideline recommendations, a DSMB has not been installed for this study.

12.4 Clinical Events Committee

Clinical events will be reviewed and adjudicated by an independent Clinical Events Committee (CEC) organized by Cardialysis. For detailed information regarding the definitions of clinical events, please refer to the Appendix. Further details on endpoint subcategories and other CEC processes are outlined in the CEC charter.

12.5 Contract Research Organization (CRO)

The local CRO will be responsible for project management, EDC development, data management, site management and monitoring, safety reporting, generating lists for Cardialysis (e.g., for the CEC) based on EDC SAE reports and any other identified SAEs or triggers, performing statistical analysis of the study data, and transferring data to Cardialysis.

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Fengsheng Chuangjian Building
763 Mengzi Road, Huangpu District
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INFORMED CONSENT FORM

Study Title: A Chinese Registry Study on Coronary Calcified Nodules Evaluated by Intravascular Imaging (CN-IVI Registry)

Version: 1.0
Date: pending

Principal Investigator at this site: Junbo Ge
Institution: Zhongshan Hospital, Fudan University
Contact Phone Number: 86 13816767665

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1. Invitation and Study Purpose

You are invited to take part in a research study because you have a specific type of coronary artery plaque called a "calcified nodule," which was found during your recent heart catheterization procedure using advanced imaging inside your blood vessels (IVUS or OCT).

Calcified nodules are a form of hardened plaque that can sometimes be challenging to treat. However, doctors do not yet fully understand their long-term behavior or the best way to manage them. The purpose of this registry study is to collect information about patients like you who have these nodules. By observing your health status and treatment results over time, we hope to learn more about the natural course of these nodules and which treatments lead to the best outcomes for future patients.

Approximately **500 patients** across about **20 hospitals in China** will be enrolled in this study.

2. What Will Happen in This Study?

If you agree to participate, your involvement will be as follows:

- **Your Standard Care:** The treatment you receive for your heart condition will be decided solely by you and your doctor. This study **does not change your treatment plan.** Whether your nodule is treated with angioplasty, a stent, or not at all, it is a decision based on your medical needs, not this study.
- **Data Collection:** We will ask for your permission to collect the images and data from your coronary angiography and intravascular imaging procedure that have already been done.
- **Medical Record Review:** Researchers will review your hospital medical records to collect information about your health, the procedures you underwent, and the results.
- **Follow-Up Visits:** You will be asked to participate in follow-up visits or phone calls with the study team at **1 year, 2 years, and 3 years** after your initial procedure. During these contacts, we will ask about your health, any hospital visits, medications, and how you are feeling. These can often be done over the phone to make it easier for you.

Your total participation in this study will last for **3 years.**

3. Risks and Discomforts

Since this is an observational study that does not involve any experimental procedures or changes to your standard medical care, the risks to you are minimal.

- The main risk is the potential **loss of privacy and confidentiality** of your personal health information. We have strict measures in place to protect your data (see Confidentiality section).
- The follow-up phone calls may take some of your time.

4. Benefits

You may not receive any direct benefit from participating in this study. However, the information learned from this research may help doctors better understand how to treat patients with calcified nodules in the future, which could benefit others with your condition.

5. Alternatives

Your alternative is to not participate in this registry. This decision will not affect the medical care you receive now or in the future in any way.

6. Confidentiality

Your privacy is very important to us. All information collected about you for this study will be kept strictly confidential. Your name and personal identifying information will be replaced with a unique code number. Any documents or databases used for the research will use this code number instead of your name. The list connecting your name to this code will be kept secure and separate from the research data.

Your records may be reviewed by authorized representatives of the sponsor (Zhongshan Hospital) or regulatory authorities to ensure the study is conducted properly, but they will also be required to keep your information confidential.

7. Costs and Compensation

There are no costs to you for participating in this study. You will not be paid for your participation.

8. Voluntary Participation

Taking part in this study is entirely your choice. Your decision to participate or not will not affect your relationship with your doctors or the quality of your medical care now or in the future. You have the right to withdraw from the study at any time, for any reason, without any penalty or loss of benefits to which you are otherwise entitled.

9. Questions and Contact Information

If you have any questions about this study now or in the future, you can contact:

- **Your Study Doctor:** , Phone:
- **Institutional Review Board (IRB)/Ethics Committee:** , Phone: Email:
-

You will receive a copy of this signed and dated informed consent form to keep.

Statement of Consent

I have read this consent form, or it has been read to me. I have had the opportunity to ask questions, and all my questions have been answered to my satisfaction. I voluntarily agree to participate in this study.

Subject Signature: _____
Printed Name: _____
Date (YYYY-MM-DD): _____

Witness Signature (if required): _____
Printed Name: _____
Date (YYYY-MM-DD): _____

Investigator/Designee Signature: _____
Printed Name: _____
Date (YYYY-MM-DD): _____