A prospective, multicenter study to evaluate the performance and safety of Comet™ Pressure Guidewire in the measurement of FFR in Chinese patients

COMET CHINA

S2434

CLINICAL INVESTIGATION PLAN

Sponsored By

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Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
AA	Jan, 25, 2019	90702637_Rev/Ver AJ	N/A	N/A	First release
AB	Apr, 29, 2019	90702637_Rev/Ver AL	Inclusion criteria	Limited patient age must less than or equal to 75 years	Clear description
			Data collection	Identify the data collection time rang after procedure	Clear description

2 Protocol Synopsis

<table>
<tr><td colspan="2">A prospective, multicenter study to evaluate the performance and safety of Comet™ Pressure Guidewire in the measurement of FFR in Chinese patients

COMET CHINA</td></tr>
<tr><td>Objective</td><td>To evaluate the performance and safety of Comet™ Pressure Guidewire in FFR (Fractional Flow Reserve) measurements in Chinese population.</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>The Comet™ Pressure Guidewire, FFR Link and iLab™ Polaris Multi-Modality Guidance System is indicated for use to measure physiological parameters in the coronary and peripheral blood vessels.</td></tr>
<tr><td>Test Device</td><td>Comet™ Pressure Guidewire, FFR Link and iLab™ Polaris Multi-Modality Guidance System (Boston Scientific)</td></tr>
<tr><td>Controlled Device</td><td>Pressure Wire Certus® , RadiAnalyzer® System (St. Jude Medical Systems AB, Uppsala, Sweden)</td></tr>
<tr><td>Test Device Sizes</td><td>1 iLab™ Polaris Multi-Modality Guidance System
2 FFR Link
3 Comet™ Pressure Guidewire
<table>
<tr><th>Characteristic</th><th>Comet Pressure Guidewire</th></tr>
<tr><td>Labeled diameter</td><td>0.014”</td></tr>
<tr><td>Wire length</td><td>185 cm</td></tr>
<tr><td>Flexible portion of wire length</td><td>33 cm</td></tr>
<tr><td>Tip length</td><td>3 cm</td></tr>
<tr><td>Tip shape</td><td>Straight</td></tr>
</table></td></tr>
<tr><td>Controlled Device Size</td><td>1 RadiAnalyzer® System
2 Pressure Wire Certus®
<table>
<tr><th>Characteristic</th><th>Pressure Wire Certus</th></tr>
<tr><td>Labeled diameter</td><td>0.014”</td></tr>
<tr><td>Wire length</td><td>175 cm</td></tr>
<tr><td>Flexible portion of wire length</td><td>31 cm</td></tr>
<tr><td>Tip length</td><td>3 cm</td></tr>
<tr><td>Tip shape</td><td>Straight</td></tr>
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</table>

Study Design	A prospective, open-label, multi-center study designed to validate the agreement of Comet™ Pressure Guidewire and Pressure Wire Certus® in FFR measurements
Study Population	Patient with stable angina or any form of non-ST elevation acute coronary syndrome, who are scheduled for diagnostic angiography and pressure wire assessment, and signed the informed consent, will be screened for enrollment in this study.
Planned Number of Subjects	100 paired measurements from up to 50 subjects
Planned Number of Sites/ Countries	At least 2 sites in China
Follow-up Schedule	Subject follow-up will end at hospital discharge post FFR measurement
Study Duration	18 months
Primary endpoint	Acceptable agreement between Comet™ Pressure Guidewire and Pressure Wire Certus® in FFR measurements
Secondary endpoint	Safety endpoints: • Pressure wire-related death • Pressure wire-related cardiac tamponade • Pressure wire fracture • Pressure wire-related unanticipated adverse event (UADE)
Method of Assigning Patients to treatment	Patients who sign the Ethics Committee-approved Informed Consent Form (ICF), and have met all inclusion criteria and none of the exclusion criteria, are eligible to be enrolled in the clinical study. All eligible subjects will receive FFR measurements simultaneously by both Comet™ Pressure Guidewire and pressure wires Certus®. For the two pressure wires which should be passed the target lesion first, each site will be provided a randomized digital table with a 1:1 ratio at target vessel level.
Medication treatment	1) Maximal hyperemia will be induced by intravenous adenosine-5'-triphosphate (ATP) via the median cubital vein. 2) Subjects will receive routine drug treatment required for diagnostic angiography and PCI according to the standard clinical practice in China.
✓ **FFR**	FFR system set-up

Measurement method	✓ Set up both FFR systems according to their respective DFUs FFR measurement: based on the current FFR guidelines in China*, following steps of FFR measurement are required: 1) The two sensors of Comet wire and Certus wire should be placed at same location – 3 to 5cm distal to the target lesion. 2) Coronary infusion of Nitroglycerine prior to pressure measurement. 3) Both baseline Pd/Pa will be recorded. 4) Maximal hyperemia will be induced by intravenous adenosine-5'-triphosphate (ATP) via the median cubital vein. 5) FFR values measured by both systems should be recorded during hyperemia for each target lesion. 6) After FFR measurement, withdraw the pressure wire and record 'Pd/Pa' when the sensor is at the tip of guiding catheter for calculating the drift. (Drift is equal to the observed 'Pd/Pa' minus 1) **Special requirement** Revascularization decision-making is based on FFR value achieved by Pressure Wire Certus®. **The Chinese expert consensus on the clinical application of coronary fractional flow reserve Chinese Journal of Cardiology. 2016,44(4):292-297.*
Inclusion Criteria	<u>General Inclusion Criteria:</u> • Patient must be at least 18 years old and less than or equal to 75 years of age • Patient or his/her legally-authorized representative agrees to sign the EC-approved ICF prior to the procedure • Patient with stable angina or any form of non-ST elevation acute coronary syndrome and is clinically indicated of intra-coronary diagnostic angiography and FFR assessment <u>Angiographic Inclusion Criteria:</u> • Moderate stenosis (30% to 70% diameter stenosis by visual estimation) is detected at diagnostic angiography
Exclusion Criteria	<u>General Exclusion Criteria:</u> • Patients unable to provide informed consent • Patients in pregnant state • Known renal insufficiency or failure (serum creatinine level of > 2.5 mg/dL, or on dialysis) • Allergy to the contrast • Significant arrhythmia, such as II degree or above of atrioventricular block, Sick sinus syndrome, ventricular tachycardia • Spastic bronchial asthma • ST elevationacute coronary syndrome • Hemodynamic instability • Contraindications to nitroglycerin or ATP • Current participation in another investigational drug or device clinical study that may affect the FFR measurements <u>Angiographic Exclusion Criteria:</u> • Chronic total occlusion (CTO) lesion • Severe vessel tortuosity at the stenotic segments

	• Culprit vessel of non-ST-segment elevation acute myocardial infarction
Statistical Test Method	Bland-Altman plot will be used to assess the agreement between Comet™ Pressure Guidewire and Pressure Wire Certus® in FFR measurements.
Sample Size Parameters	• Pre-defined agreement limits = [-0.08, 0.08] • Expected paired mean difference = 0.0013 • Expected paired standard deviation (SD) = 0.03 • Two-sided significance level=5% (alpha) • Power > 80% • A minimum of 100 paired measurements* from 50 patients are needed for this study **Lu MJ, Zhong WH, Liu YX, Miao HZ, Li YC, Ji MH (2016) Sample size for assessing agreement between two methods of measurement by Bland-Altman method. The International Journal of Biostatistics 12: issue 2 (8pp)*
Acceptable criteria	Agreement between the two methods of measurement will be confirmed if both conditions are met: 1) The mean paired difference is within +/- 0.005 # 2) The limits of agreement (defined as the mean observed difference +/- 1.96* observed SD) is within the pre-defined agreement limits of [-0.08, 0.08] # # *Nick Curzen, Rod Stables. Randomised Comparison of Simultaneous Data from two Different Pressure Wires: the COMET trial(NCT02578381)*

3 Table of Contents

2.1. *Table of Figures*

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4 Introduction

4.1 Background

Although angiography is an established invasive approach for assessment of coronary artery disease (CAD), its ability to evaluate the functional significance of stenosis is limited [1,2].

Fractional flow reserve (FFR) technology is based on the concept that the functional significance of a lesion; i.e., whether the lesion can cause ischemia, can provide information as to whether the lesion should be treated. The functional significance of a lesion in the case of FFR is determined based on the pressure drop across the lesion. Pressure is measured at the descending aorta (Pa) and distal to the lesion (Pd). The ratio of Pd/Pa is known as FFR value. FFR value provides information on the functional significance of coronary artery stenosisand can be used as a diagnostic tool, to facilitate its treatment decision-making.

Tonino PA, et al[2] found angiography is inaccurate in assessing the functional significance of a coronary stenosis when compared with the FFR, not only in the 50% to 70% category but also in the 70% to 90% angiographic severity category. Among all stenosis with an angiographic severity of 50% to 70%, 65% were functionally nonsignificant and 35% were functionally significant by the FFR. Even in more severe stenosis between 71% and 90% angiographic stenosis severity, 20% of the lesions did not induce reversible myocardial ischemia as established by a FFR value above the ischemic threshold. Therefore, in patients with multivessel CAD, whether or not taking into account clinical data, one cannot rely on the angiogram to identify ischemia-producing lesions.

Tonino PA et al[3] also demonstrated the importance of FFR in patients with multivessel coronary disease undergoing revascularization in the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. This prospective, multicenter, international trial randomly assigned 1005 patients with multivessel coronary artery disease to either PCI guided by FFR (PCI if FFR $\leqslant$0.8) or by angiography alone. As compared with the standard strategy of PCI guided by angiography, FFR guided PCI significantly reduced the rate of the primary composite end point of death, myocardial infarction, and repeat revascularization at 1 year (18.3% in the angiography group and 13.2% in the FFR group, P = 0.02).

Subsequently, the FAME 2 clinical trial [4] was designed to test whether optimal medical therapy alone was superior to FFR-guided PCI plus optimal medical therapy in patients with stable coronary disease. Recruitment was halted early in this prospective, multi-center, international trial of 1220 patients (of whom 888 underwent randomization) due to an early finding of a significant difference between the groups in the primary endpoint event (death from any cause, myocardial infarction, or unplanned hospitalization leading to urgent revascularization). The PCI group had a primary event at a rate of 4.3% as compared with the medical therapy group that had an event rate of 12.7% (HR with PCI: 0.32; 95% CI: 0.19 – 0.53; $p < 0.001$). Of note, a lower rate of urgent revascularization in the PCI group drove this

difference (1.6 vs 11.1%; HR: 0.13; 95% CI: 0.06 – 0.30; p < 0.001). Recently, the 2-year results of FAME 2 showed similar primary endpoint trajectories (8.1% event rate for the PCI group vs 19.5% event rate for the medical therapy group; HR: 0.39; 95% CI:0.26 – 0.57; p < 0.001), driven by urgent revascularization (4.0% in the PCI group vs 16.3% in the medical therapy group; HR: 0.23; 95% CI: 0.14 – 0.38; p < 0.001)[5].

FFR has been also shown to be an effective method for guiding revascularization in other studies [6–10]. Therefore, it has received a class IA recommendation from the European Society of Cardiology for identifying hemodynamically relevant coronary lesions when evidence of ischemia is not available and a class IIA recommendation from the American College of Cardiology for the assessment of angiographic intermediate coronary lesions (50-70% diameter stenosis) and for guiding revascularization decisions in patients with CAD [11,12].

4.1.1 preclinical study

1）A preclinical study (91050762) was conducted to assess Comet thrombogencity. The purpose of the study was to evaluate the thrombogenic potential risk of a the Comet Pressure Guidewire compared to the Kinetix Guidewire under non-anticoagulated conditions in the common swine model.

During the explantation of the test devices, no thrombus was observed on any of the test devices and no occlusions of the arteries were observed. During the explantation of the control devices minimal thrombus was observed on one of the control devices. No occlusions of the arteries were observed. Images were obtained of each treatment site and device. The limited necropsies for both animals no thromboembolisms were present in the heart or lungs.

Based on the results of this study, the Comet Pressure Guidewire (test) had similar thromboresistance characteristics compared to the Kinetix Guidewire (control).

2）A GLP *in vivo* preclinical study was conducted to evaluate acute performance of the Comet Pressure Guidewire using a series of performance characteristics and evaluated acute pressure measurements (Pd) using the iLab™ Polaris Multi-Modality Guidance System and Comet Pressure Guidewire compared to invasive aortic blood pressure (Pa) in the vasculature of a swine model.

Test Articles met the acceptance criteria of a pressure accuracy specification $|Pd - Pa| \leq 8$ mm Hg. This acceptance criteria is derived from IEC 60601-2-34: 2011 accuracy specification of ± 4 mmHg for each System (i.e., Invasive blood pressure monitor (Pa) and iLab™ Polaris Multi-Modality Guidance System with Comet Pressure Guidewire (Pd)). Considering that each system has an accuracy requirement of ± 4 mmHg, the combined tolerance is ± 8 mmHg.

The absence of adverse events and the acceptable delivery and performance of the device support the safety and performance of the Comet Pressure Guidewire and iLab Polaris.

4.1.2 Clinical trial

The COMET Trial [13] assessed diagnostic and drift performance of FFR devices in a 100-patient randomized controlled trial (RCT) that compared the Comet Pressure Guidewire to the Pressurewire Certus (St. Jude) by allocating patients to simultaneous paired readings using three groups (Comet-Comet [n=37], Certus-Certus [n=34], Comet-Certus [n=35]). The COMET trial was conducted at two sites in the United Kingdom. For each vessel, four pressure readings were taken with the pressure wires in the same position: equalization at the guide tip catheter; baseline Pd/Pa in the distal vessel; FFR in the target measurement site (at steady state maximum hyperemia using intravenous adenosine); and final Pd/Pa at the guide catheter tip (to measure drift). Drift estimations were made in 142 vessels for Comet Pressure Guidewire and 137 for Pressurewire Certus.

No significant difference in the performance between the two pressure wires was observed. The absolute magnitude of the difference between the measurements of the Comet Pressure Guidewire and the Pressure wire Certus is no different than the magnitude of difference between two measurements of Pressure wire Certus, with a Comet-Certus median difference of 0.01(n=108 paired readings) and Certus-Certus median difference of 0.015 (n=90 paired readings; p=0.61 for difference between the two groups). See Figure4.1- 1 for graphs of paired readings. In addition, both the Comet Pressure Guidewire and Pressure wire Certus exhibit a small degree of drift that is not significantly different from the other (Comet median drift = 0.02, standard deviation 0.039; Certus median drift = 0.02, standard deviation 0.031; p=0.14).

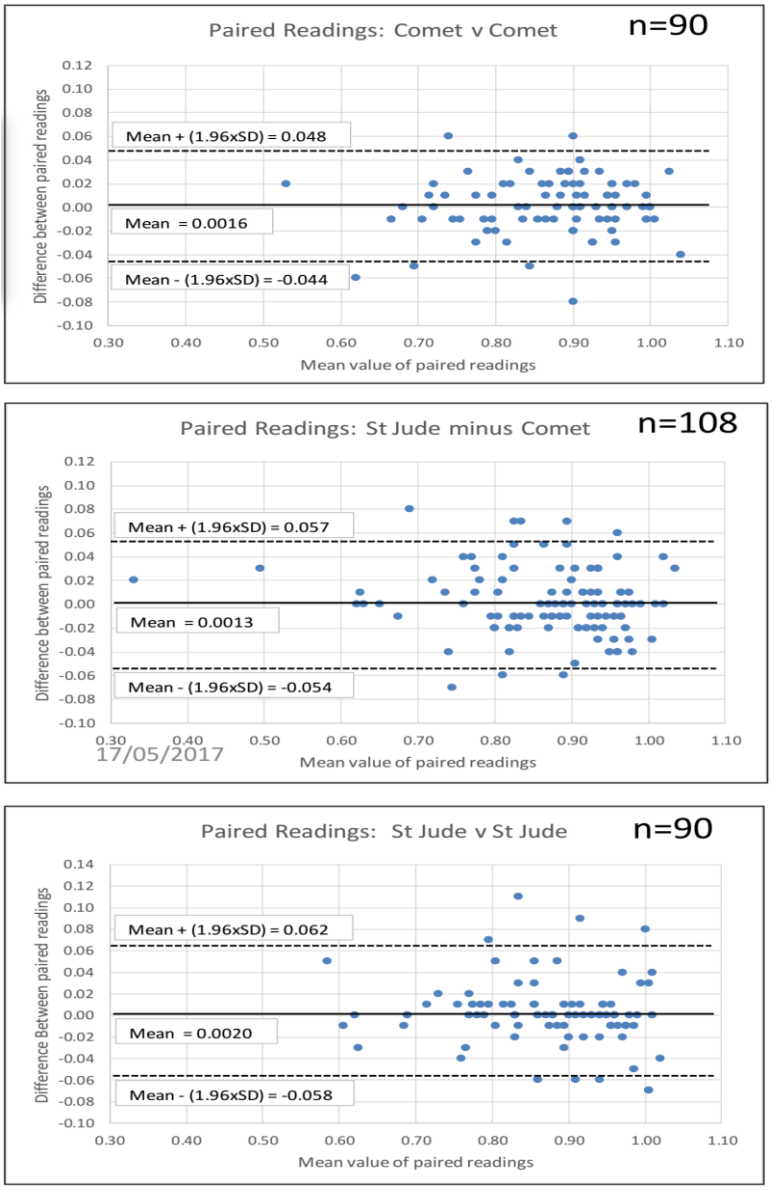


Figure4.1- 2 Observed delta

Observed Delta in FFR Reading in Comet-Comet (top), Comet-Certus(middle), and Certus-Certus (bottom) Groups

4.2 Study Rationale

The objective of this study is to evaluate the performance and safety of Comet™ Pressure Guidewire in FFR (Fractional Flow Reserve) measurements in Chinese population in order to support the regulatory submission in China.

5 Device Description

5.1 Test devices

5.1.1 Comet Pressure Guidewire

The Comet Pressure Guidewire is a single use, hydrophilic-coated, steerable wire with a custom optical cable. A pressure sensor is mounted approximately 3 cm from the distal end of the radiopaque and shapeable straight tip. For product specifications, including wire diameter, length, and radiopaque tip length, please refer to the product labeling/DFU.

The Comet Pressure Guidewire is indicated to direct a catheter through a blood vessel and to measure physiological parameters in the coronary blood vessels.

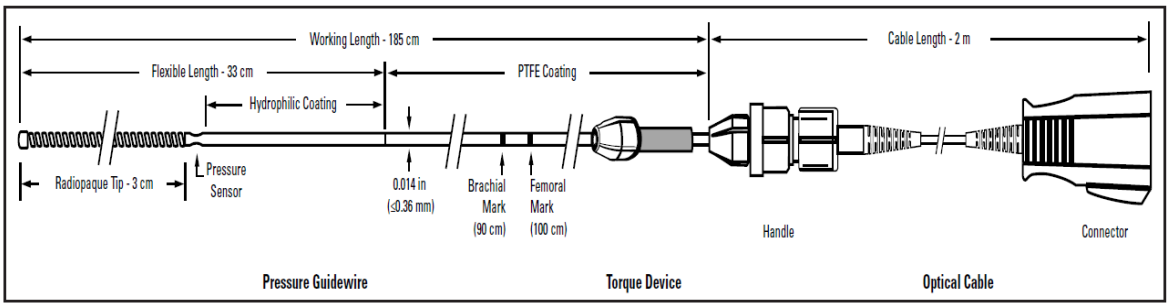


Figure 5.1- 1 Comet Pressure Guidewire

The characteristics of the **Comet Pressure Guidewire** are described in **Table 5-1.**

Table 5-1: Comet Pressure Guidewire Description

Characteristic	Description
Labeled diameter	0.014”
Wire length	185 cm
Flexible portion of wire length	31 cm
Tip length	3 cm
Tip shape	Straight

5.1.2 FFR link

FFR Link: The FFR Link (see Figure 5.1- 2 transmits aortic (Pa) and distal (Pd) blood pressure under the control of the Polaris software or Hemodynamic System with Licensed FFR Calculation Module. The FFR Link is a hardware module that is installed with either an existing or a new iLab Polaris system. In this use scenario, the FFR Link can be used to obtain the pressure measurement from the Comet Pressure Guidewire and provide an analog Pd out signal.

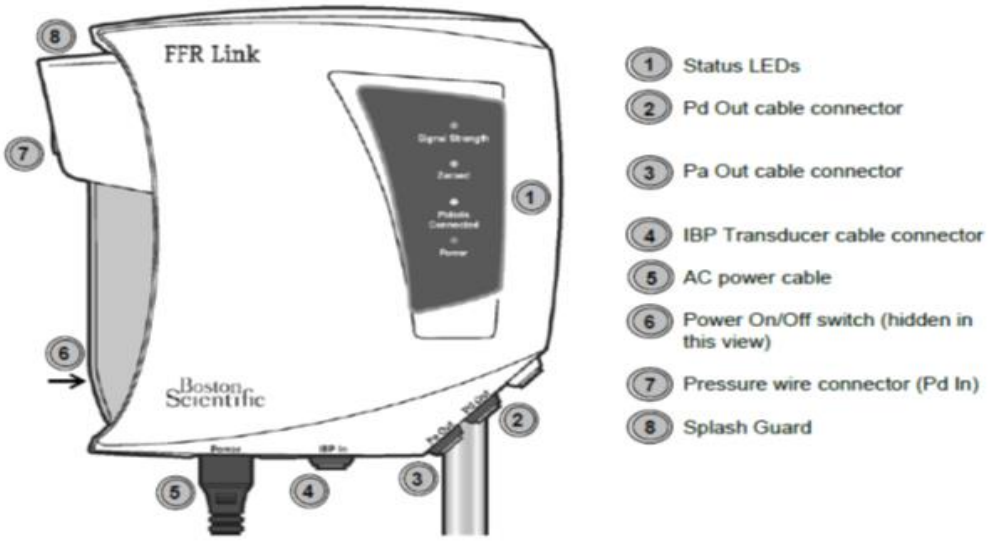


Figure 5.1- 3 FFR Link

5.1.3 iLab™ Polaris Multi-Modality Guidance System

The iLab Polaris Multi-Modality Guidance System is an upgrade to the iLab Ultrasound Imaging System to add a Fractional Flow Reserve (FFR) modality to the existing ultrasound imaging modality (IVUS).

The iLab Polaris System is designed to provide both ultrasound imaging and fractional flow reserve modalities. Only one modality can be used at a time and are independent of one another.

The system set up shall follow the instructions in the DFU. And the connection is shown in the Figure 5.1- 4**.**

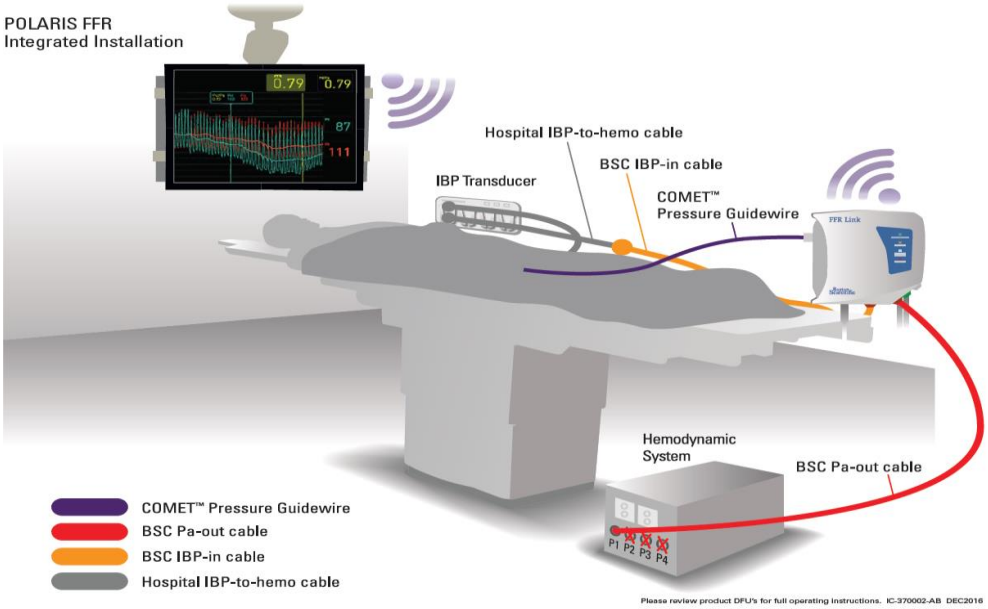
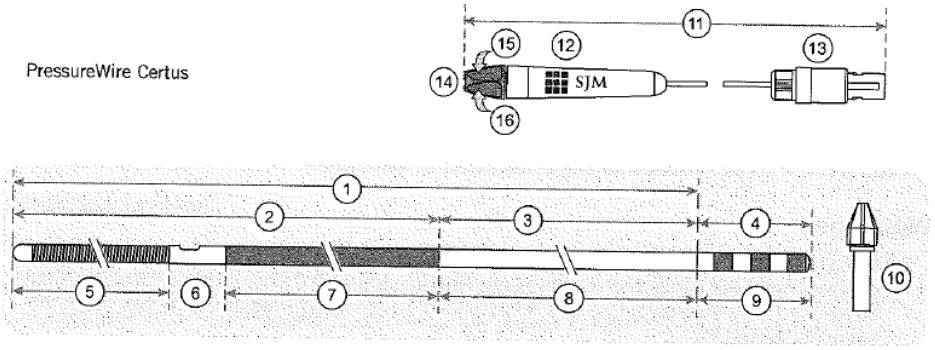


Figure 5.1- 5 System set-up

5.2 *Controlled device*

5.2.1 PressureWire Certus



PressureWire Certus is a 0.014'' guidewire with an integrated sensor element at the tip to enable measurements of physiological parameters. Pressurewire is available in different lengths. Please refer to the label for information about pressureWire length and thermos compatibility.

5.2.2 RadiAnalyzer System

RadiAnalyzer is a diagnostic computer designed to compute, record and display information from PressureWire and other external transducers.

6 Study Objectives and Endpoints

6.1 study objectives

The primary objective of this study is to evaluate the performance and safety of Comet™ Pressure Guidewire in FFR (Fractional Flow Reserve) measurements in Chinese population.

6.2 Study endpoints

6.2.1 The primary efficacy endpoint:

The primary efficacy endpoint is the acceptable agreement between Comet™ Pressure Guidewire and Pressure Wire Certus® in FFR measurements.

Notes

Agreement between the two methods of measurement will be confirmed if both conditions are met:

- The mean paired difference is within +/- 0.005 [13]
- The limits of agreement (defined as the mean observed difference +/- 1.96* observed SD) is within the pre-defined agreement limits of [-0.08, 0.08] [13]

6.2.2 The Secondary endpoint:

The safety endpoint is the rate of following major adverse events:

- Pressure wire-related death
- Pressure wire-related cardiac tamponade
- Pressure wire fracture
- Pressure wire-related unanticipated adverse event (UADE)

7 Study Design

The COMET China study is a prospective, open-label, multi-center study designed to validate the agreement of Comet™ Pressure Guidewire and Pressure Wire Certus® in FFR measurements. Patient with stable angina or any form of non-ST elevation acute coronary syndrome, who are scheduled for diagnostic angiography and pressure wire assessment, and signed the informed consent, will be screened for enrollment in this study.

7.1 Scale and Duration

The COMET China trial will be conducted in at least 2 sites in Mainland China with planned enrollment of up to 50 subjects.

The study is planned to have approximately 6 months of enrollment.

All subjects will be screened according to the protocol inclusion and exclusion criteria. All eligible subjects will receive Pd/Pa and FFR measurements simultaneously by both Comet™ Pressure Guidewire and pressure wires Certus®. For the two pressure wires which should be passed the target lesion first, each site will be provided a randomized digital table with a 1:1 ratio at target vessel level. Subject follow-up will end at hospital discharge post FFR measurement.

The study will be considered complete after all subjects have discharged from hospital, or withdrawn from the trial (due to death or having been lost to follow-up).

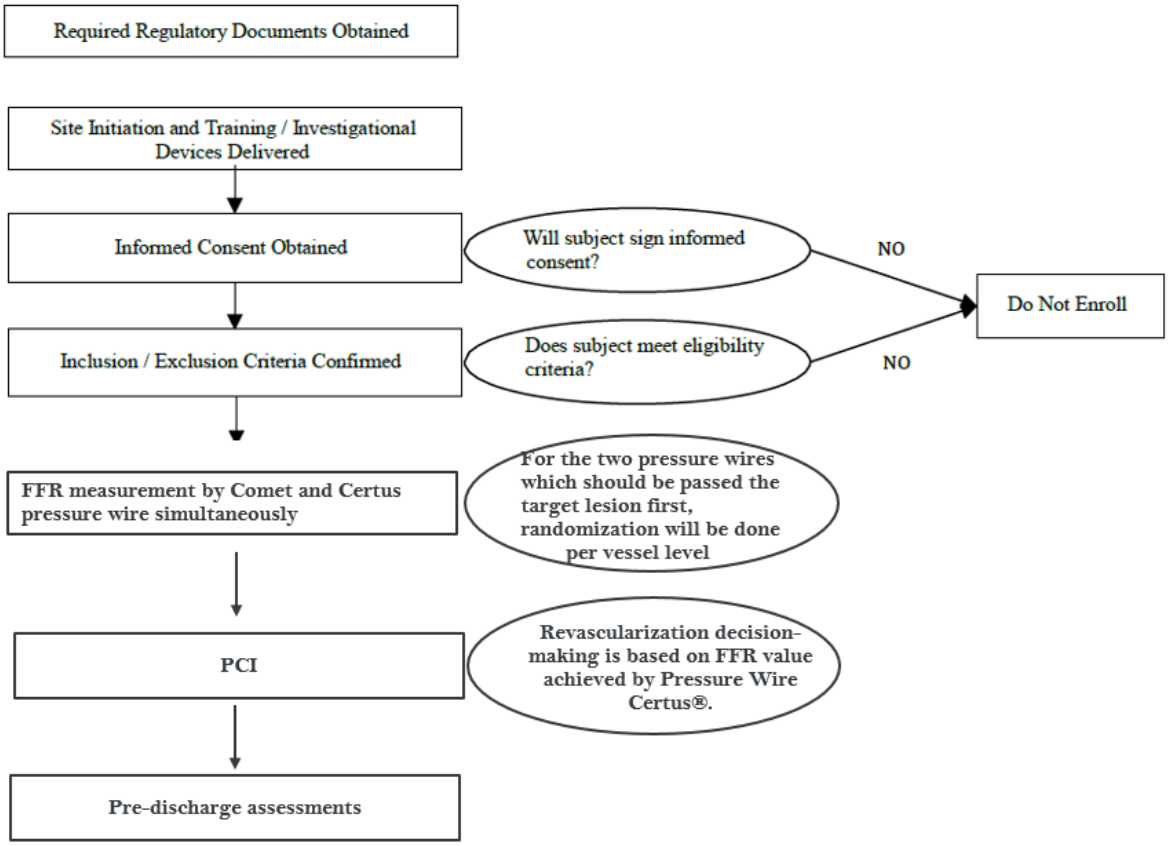


Figure 7.1- 1 Study design

7.2 Treatment Assignment

Patients who sign the Ethics Committee-approved Informed Consent Form (ICF), and have met all inclusion criteria and none of the exclusion criteria, are eligible to be enrolled in the clinical study. All eligible subjects will receive Pd/Pa and FFR measurements simultaneously by both Comet™ Pressure Guidewire and pressure wires Certus®. For which wire should be passed the target lesion first, randomization will be performed as described in chapter 7.1.

7.2.1 Treatment and Control

Subjects enrolled in this clinical trial will not be randomized, and there is no control group in this study. All the patients will receive measurements by both Comet™ Pressure Guidewire and pressure wires Certus® at the same time. For which wire should be passed the target lesion first, each site will be provided a randomized digital table with a 1:1 ratio at target vessel level.

7.3 Justification for the Study Design

The Comet Pressure Guidewire received FDA clearance on 06-Oct-2015 and CE Mark on

10-Feb-2016. FDA clearance for the FFR Link was received on 06-Oct-2015 and CE Mark in December 2015. Date of CE Mark for iLab Polaris Multi-Modality Guidance System (IVUS and FFR Modality): Dec 2015.
This trial is designed to evaluate the performance and safety of Comet™ Pressure Guidewire in FFR (Fractional Flow Reserve) measurements compare to PressureWire Certus in Chinese population.

Subjects will receive routine drug treatment required for diagnostic angiography and PCI according to the standard clinical practice in China. And FFR measurement will be based on the current FFR guidelines in China.

8 Subject Selection

8.1 Study Population and Eligibility

Patient with stable angina or any form of non-ST elevation acute coronary syndrome, who are scheduled for diagnostic angiography and pressure wire assessment, and signed the informed consent, will be screened for enrollment in this study. Clinical and angiographic inclusion and exclusion criteria for the COMET China trial are included in Section 8.2 and Section 8.3 respectively. Prior to enrollment in the trial, a subject should meet all of the clinical and angiographic inclusion criteria and none of the exclusion criteria.

8.2 Inclusion Criteria

Subjects who meet all of the following criteria (see Table 8.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 8.3) is met.

Table 8.2-1: Inclusion Criteria

Inclusion Criteria	General Inclusion Criteria: • Patient must be at least 18 years old and less than or equal to 75 years of age • Patient or his/her legally-authorized representative agrees to sign the EC-approved ICF prior to the procedure • Patient with stable angina or any form of non-ST elevation acute coronary syndrome and is clinically indicated of intra-coronary diagnostic angiography and FFR assessment Angiographic Inclusion Criteria: Moderate stenosis (30% to 70% diameter stenosis by visual estimation) is detected at diagnostic angiography

8.3 Exclusion Criteria

Subjects who meet any one of the following criteria (Table 8.3-1) cannot be included in this study or will be excluded from this clinical study.

Table 8.3-1: Exclusion Criteria

Exclusion Criteria	General Exclusion Criteria: • Patients unable to provide informed consent • Patients in pregnant state • Known renal insufficiency or failure (serum creatinine level of > 2.5 mg/dL, or on dialysis) • Allergy to the contrast • Significant arrhythmia, such as II degree or above of atrioventricular block, Sick sinus syndrome, ventricular tachycardia • Spastic bronchial asthma • ST elevation coronary syndrome • Hemodynamic instability • Contraindication to nitroglycerin or ATP • Current participation in another investigational drug or device clinical study that may affect the FFR measurements Angiographic Exclusion Criteria: • CTO lesion • Severe vessel tortuosity at the stenotic segments • Culprit vessel of non-ST-segment elevation acute myocardial infarction

9 Subject Accountability

9.1 Point of Enrollment

Subject, who has signed the IRB/IEC-approved study ICF, and has met all inclusion criteria and none of the exclusion criteria, will be considered eligible to be enrolled in the trial. Enrollment occurs at the time of advancement of either Comet™ Pressure Guidewire or PressureWire Certus® into the guide catheter.

9.2 Withdrawal

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) of withdrawal shall be recorded. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

9.3 End-of-Study Definition

The clinical trial is considered completed when the last participant's discharge from hospital post FFR measurement.

9.4 Enrollment controls

Up to 50 subjects are needed to provide 100 paired measurements for assessing the primary endpoint. The enrollment cap for each participating center is 35 subjects.

10 Study Methods

10.1 Data Collection

The data collection schedule is shown in Data Collection Schedule

Table 10.1-1: Data Collection Schedule

Procedure/Assessment	Screening (≤ 14 days prior to index procedure)	Enrollment	Index Procedure	Pre-hospital Discharge
In-person Visit	X	X	X	X
Informed Consent process, including informed consent signature date	X			
Demographics (including date of birth, gender, and race and ethnicity)	X			
Physical Assessment, including weight, height and blood pressure	X			
Medical History (including, concomitant diseases, concomitant medication and medical treatments)	X[d]	X[d]	X[d]	X[d]
12-lead ECG	X			X[f]
Routine Laboratory (including serum creatinine, myocardial enzyme, CBC with Hemoglobin and Hematocrit, pregnancy tests)[a]	X			X[e]
Angiographic assessment		X[b]	X	
FFR measurement [C]			X	
Procedure Assessment (including stenting information)			X	
Adverse Events and Device Deficiency Assessment			X	X

X = required;
a: pregnancy test is required within 72 hours prior to index procedure for potential child-bearing women.
b: According to Angiographic Inclusion criteria and exclusion criteria.
c: both Comet and Certus pressure guidewire
d: Antithrombotic, antiplatelet medications, and medications for FFR measurement (adenosine-5'-triphosphate (ATP), nitroglycerine).
e: myocardial enzyme(12 to 24 hours post FFR procedure)
f : within 24 hours post FFR procedure

10.2 Study Candidate Screening

Patient with stable angina or any form of non-ST elevation acute coronary syndrome, who are scheduled for diagnostic angiography and pressure wire assessment, will be asked to sign the informed consent form (ICF) before participating in any screening procedure. After signing the ICF, the subject will receive a screening number and will be documented in a screening log. Each clinical investigator must keep a log of all screened subjects, including both eligible and non-eligible subjects (screening failures).

10.3 Informed Consent

Before any study specific tests or procedures are performed, subjects who meet the clinical inclusion criteria will be asked to sign the IRB/IEC-approved study ICF. Subjects must be given ample time to review ICF and have questions answered before signing ICF.
Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, coronary angiography may demonstrate that the subject is not a suitable candidate for the clinical trial.

10.4 Screening (Up to 14 days prior to index procedure)

After a subject has signed the IRB/IEC-approved study ICF, the screening process may begin. The screening process will be used to determine the inclusion or exclusion of a subject in the study. This process includes the investigator's assessment of subject's medical records and diagnosis, and following pre-procedure data must be collected within 14 days prior to the index procedure (unless otherwise specified), for all subjects:

- Confirmation of clinical eligibility criteria (inclusion and exclusion criteria)
- Demographics including age, gender, and races others than Han (unless restricted by local laws)
- Physical assessment, including weight, height and blood pressure
- Medical history (including concomitant diseases, concomitant medication and medical treatments)
- Routine laboratory tests
  - ✓ Serum creatinine
  - ✓ Complete blood count (CBC) , Hemoglobin and Hematocrit
  - ✓ Myocardial enzyme
  - ✓ Pregnancy test for females of child-bearing potential with analysis per local practice (serum and/or urine) is required within72 hours prior to the index procedure
- Baseline 12-lead ECG

10.5 Required Concomitant Medications

Protocol-required concomitant medications must be reported in the electronic case report form (eCRF) from the time of the pre-procedure visit through the discharge from hospital. Other concomitant medications also should be reported according to pertinent China laws and regulations. Additional concomitant medications may be prescribed at the discretion of the investigator based on the standard clinical practice.

10.5.1 Prior and post to the index procedure

Medications related to antithrombotic, antiplatelet medications prior and post to the index procedure will be prescribed based on standard clinical practice or at discretion of the treating physician.

10.5.2 In the Catheterization Laboratory

- At the time of the procedure, subjects should receive an intra-arterial bolus of heparin (usually 3000-5000 I.U.), or alternate anticoagulants as substitutes for heparin if justified by individual subject conditions.
- Coronary injection of nitroglycerine (total: 50-100μg) prior to pressure measurement will be needed. The dosage can be adjusted according to the subject's blood pressure.
- Maximal hyperemia will be induced by intravenous adenosine-5'-triphosphate (ATP) via the median cubital vein at ⩾160 μg/kg/min, and <180 μg/kg/min.

10.6 Enrollment & Index Procedure

Investigators will manage the cardiovascular risk factors and comorbidities for all subjects according to standard care. Coronary angiography must be performed using standard techniques to confirm angiographic eligibility of the target lesion. Visual angiographic assessment may be used to determine if inclusion/exclusion criteria are met.

10.6.1FFR measurements

Following key points of FFR measurement are required in this study:

- The use of 6 French guiding catheters (GC) was mandated to optimize the quality of phasic pressure recording at the tip of the GC.
- Simultaneous equalization of the aortic and pressure wire tracings was performed with both pressure wire sensors at the GC tip before wires were advanced, sequentially, down the coronary vessel.
- Randomization by target vessel will be done to determine which wire to pass the target lesion first.
- The two sensors of guidewires should be placed at the same location – 3 to 5cm distal to the target lesion. Confirmation of the two sensor locations must be obtained under two orthogonal radiographic projections.
- Coronary injection of nitroglycerine (total: 50-100μg) prior to pressure measurement will be needed. The dosage can be adjusted according to the subject's blood pressure .
- Baseline recordings of Pd/Pa need to be stable for ⩾ 3 seconds
- Maximal hyperemia will be induced by intravenous adenosine-5'-triphosphate (ATP) via the median cubital vein at ⩾160 μg/kg/min, and <180 μg/kg/min. FFR values measured by both systems should be recorded during hyperemia for each target lesion at the "steady-state" at least 10 seconds of stable value during hyperemia.
- After FFR measurement, withdraw the pressure wire and record 'Pd/Pa' when the sensor is at the tip of guiding catheter for calculating the drift. The Pd/Pa need to be stable for for ⩾ 3 seconds

. (Drift is equal to the observed 'Pd/Pa' minus 1).

The following information should be recorded during the index procedure:

- Passthrough time of the target lesion of the two pressure wires (from guiding catheters tip to distal of the target lesion)
- Baseline Pd/Pa, FFR, and drift.
- Technical success (the pressure wire could be successfully passed to the desired location in the target vessel and FFR recording could be obtained) of every target lesion.
- Medications given during the procedure, including antithrombotic and antiplatelet medications, nitroglycerine and ATP
- Adverse events and device deficiency assessment during the index procedure

Following the FFR measurement, revascularization decision-making will be based on FFR value achieved by Pressure Wire Certus®.

10.6.2 End of the Index Procedure

The end of index procedure is defined as the time the guiding catheter was removed (post final angiography). The introducer(s) sheaths should be removed per standard local practice.

- Record procedure information after FFR measurement
- Collect adverse events

10.7 Post-Procedure / Pre-Discharge

The post-procedure/pre-discharge follow-up is an in-person visit and the following data will be collected:

- 12-lead ECG（within 24 hours post FFR procedure）
- Myocardial enzymes (12 to 24 hours post FFR procedure)
- Adverse events
- Medications, including antithrombotic and antiplatelet medications

10.8 Study Completion

Subject follow-up will end at hospital discharge post FFR measurement.

10.9 Source Documents

Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document.

11 Statistical Considerations

11.1 Endpoints

11.1.1 Primary Endpoint

Acceptable agreement between Comet™ Pressure Guidewire and Pressure Wire Certus® in FFR measurements

11.1.1.1 Sample Size

The sample size has been estimated based on the following assumptions[13, 14]:

- Pre-defined agreement limits = [-0.08, 0.08]
- Expected paired mean difference = 0.0013
- Expected paired standard deviation (SD) = 0.03
- Two-sided significance level=5% (alpha)
- Power > 80%

Given the above assumptions, 100 paired measurements from up to 50 patients are needed for this study.

11.1.1.2 Statistical Methods

Bland-Altman plot will be used to assess the agreement between Comet™ Pressure Guidewire and Pressure Wire Certus® in FFR measurements

11.1.2 Safety Endpoints

- Pressure wire-related death
- Pressure wire-related cardiac tamponade
- Pressure wire fracture
- Pressure wire-related unanticipated adverse event (UADE)

11.2 General Statistical Methods

11.2.1 Analysis Sets

The primary endpoints will be analyzed on a per-protocol basis. Only enrolled subjects who are measured paired FFR data with the Comet and Certus pressure wires in the target lesion will be included in the primary endpoint analysis sample. Safety analysis will be based on the ITT basis. Subjects with unpaired data will be included as appropriate, if any.

11.2.2 Control of Systematic Error/Bias

Selection of subjects will be made from the investigators' general or professional referral population. All subjects meeting the inclusion/exclusion criteria that have signed the protocol-specific ICF will be eligible for enrollment in the trial. Consecutively eligible

subjects should be enrolled into the study to minimize selection bias. In determining subject eligibility for the study, the investigator's assessment of imaging will be used.

11.2.3 Number of Subjects per Investigative Site

A maximum of 35 patients (70% of total enrolled subjects) will be recruited from one site to avoid treatment center bias and ensure homogeneous study results.

11.3 Data Analyses

Subject demographics, clinical history, risk factors, and pre-procedure lesion characteristics will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables.

11.3.1 Other Endpoints/Measurements

Clinical event rates will be presented as proportions and continuous data will be summarized by presenting sample sizes, means, standard deviations, minimums, and maximums. Point estimates and 95% confidence intervals will be provided. No statistical testing will be performed for the additional endpoints.

11.3.2 Interim Analyses

No formal interim analyses are planned for the purpose of stopping this study early for declaring effectiveness or for futility.

11.3.3 Subgroup Analyses

No subgroup analyses are planned

11.3.4 Multivariable Analyses

No multivariable analyses are planned in this study.

11.3.5 Other Analyses

No other analyses are planned in this study.

11.3.6 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analysis will be documented in an amended Statistical Analysis Plan approved prior to performing the analysis. Changes from the planned statistical methods after performing the analysis will be documented in the clinical study report along with a reason for the deviation.

12 Data Management

12.1 Data Collection, Processing, and Review

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated Rave software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Medidata EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

12.2 Data Retention

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

12.3 Core Laboratories

No Core laboratories are planned in this study.

13 Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals from IRB/EC of the revised protocol must be obtained prior to implementation.

14 Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC/REB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All protocol deviations (PDs) are classified to "major" and "minor" defined as below:

- A major PD is a protocol deviation that directly or potentially disrupts the study progress (i.e., the study design, study data and results can be compromised), ***OR*** a protocol deviation that compromises the safety and welfare of study participants.
- A minor PD is a protocol deviation that does not disrupt study progress (i.e., the study design, study data and results will not be compromised), ***AND*** does not compromise the safety and welfare of study participants.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using EDC. Sites may also be required to report deviations to the IRB/EC/REB, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

15 Device/Equipment Accountability for Products Labelled Investigational

The investigational devices/equipment shall be securely maintained, controlled, and used only in this clinical study.

Boston Scientific shall keep records to document the physical location of all investigational devices/ equipment from shipment of investigational devices from BSC or designated facility/equipment to the investigation sites until return or disposal.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices/equipment, which shall include the following

- Date of receipt
- Identification of each investigational device/piece of equipment (batch number or unique code)
- Expiry date, as applicable
- Date or dates of use

- Subject identification
- Date on which the investigational device/piece of equipment was returned/explanted from subject, if applicable
- Date of return (and number) of unused, expired, or malfunctioning investigational devices/equipment, if applicable.

16 Compliance

16.1 Statement of Compliance

This study will be conducted in accordance with ISO 14155:2011 (2nd Edition; 2011-02-01) Clinical Investigation of Medical Devices for Human Subjects- GCP, or the relevant parts of the ICH Guidelines for GCP, ethical principles that have their origins in the Declaration of Helsinki, and pertinent China's laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC/REB and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IRB/EC/REB or regulatory authority shall be followed, if appropriate.

16.2 Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC/REB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.

- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency, and provide analysis report, which includes the causality assessed by both investigator and BSC and decision on study continuance, to IRB/EC per local and/or country requirements.
- Report to sponsor, per the protocol requirements, all AEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB/EC/REB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB/EC/REB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC/REB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC/REB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.

- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

16.2.1 Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, are competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub investigator at a site, the sub investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

16.3 Institutional Review Board/ Ethics Committee

The investigational site will obtain the written and dated approval/favorable opinion of the IRB/EC/REB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB/EC/REB and/or competent authority (CA) approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF. Annual IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the sponsor.

16.4 Sponsor Responsibilities

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all

applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to Contract Research Organization (CRO), will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

16.4.1 Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment).

At the request of the investigator and while under investigator supervision, BSC personnel may operate equipment during implant or follow-up, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

16.5 Insurance

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

17 Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

18 Potential Risks and Benefits

17.1 Anticipated Adverse Events Associated with the Study Device and Procedure

The following anticipated adverse events (AE) have been identified for this study, including, but are not limited to, the following:

- Abrupt closure
- Allergic reaction
- Angina or unstable angina
- Arrhythmias
- Cardiac tamponade/pericardial effusion
- Contrast induced renal insufficiency or renal failure
- Death
- Embolism
- Exposure to biohazardous material
- Infection
- Myocardial infarction or ischemia
- Prolonged procedure
- Restenosis (reocclusion)
- Spasm
- Stroke/cerebral vascular accident (CVA)/transient ischemic attack (TIA)
- Vascular thrombus
- Vessel trauma (dissection, perforation, rupture or injury)

17.2 Risks associated with Participation in the Clinical Study

In addition to the aforementioned risks associated with the Comet pressure Guidewire, two pressure guidewires used in this study may prolong the procedure and increase the complexity of the procedure. There may be additional risks linked to the procedure, which are unforeseen at this time.

17.3 Possible Interactions with Concomitant Medication

For FFR measurement, coronary infusion of nitroglycerine and intravenous infusion of ATP are required. According to the guideline, the following anticipated adverse events (AE) have been identified, including, but are not limited to: atrioventricular block, bradycardia, sinus arrest, hypotension, chest tightness and palpitations.

17.4 Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

17.5 Anticipated Benefits

FFR measurement can assess the functional significance of coronary stenosis which have been proved to improve PCI decision-making and outcomes for patients with coronary artery disease[2-10].

17.6 Risk to Benefit Rationale

The Comet pressure wire is expected to be suitable for its intended purpose. There are no unacceptable residual risks/intolerable risks and all applicable risks have been addressed though the provision of appropriate Directions for Use (DFU). Evaluation of the risks and benefits thar are expeted to be associated with use of the Comet™ Pressure Guidewire demonstrate that when used under the conditions intended, the benefits associated with use of the Comet™ Pressure Guidewire should outweigh the risks.

18 Safety Reporting

18.1 Reportable Events by investigational site to Boston Scientific

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All AEs/SAEs
- All Investigational Device Deficiencies

- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

Any AE event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject accountability section), whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of one specific SAE.

Refer to Section 17 for the known risks associated with the study device(s).

In-patient hospitalization is defined as the subjects being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or AEs occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions. However, the original elective/planned hospitalization(s) itself should not be reported as an SAE.

18.2 Definitions and Classification

Adverse event definitions are provided in Table 18.2-1. Administrative edits were made on the safety definitions from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 18.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. **NOTE 1**: This includes events related to the investigational medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. **NOTE 2**: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.

Table 18.2-1: Safety Definitions

Term	Definition
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any 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 degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

18.3 Relationship to Study Device(s) or Procedure or Required Medications during the Procedure

The Investigator must assess the relationship of the reportable AE to the study device or procedure. See criteria in Table 18.3-1:

Table 18.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MEDDEV 2.7/3*	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Table 18.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that -the investigational device or procedures are applied to;-the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The Investigator must assess the relationship of the reportable AE to the protocol- required medication. See criteria in Table 18.3-1:

Table 18.3-2: Criteria for Assessing Relationship of Protocol- required Medication to Adverse Event

Classification	Description
Not Related	Relationship to the protocol- required medication can be excluded when: - the event is not a known side effect of the medication category the protocol- required medication belongs to or of similar medication; - the event has no temporal relationship with the use of the protocol- required medication; - the serious event does not follow a known response pattern to the protocol- required medication (if the response pattern is previously known) and is biologically implausible; - the discontinuation of protocol- required medication use or the reduction of the dose of protocol- required medication - when clinically feasible – and reintroduction of its use (or increase of the dose of protocol- required medication), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the protocol-required medication; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of protocol- required medication and the serious event.
Unlikely Related	The relationship with the use of the protocol- required medication seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be

	obtained.
Possibly Related	The relationship with the use of the protocol- required medication is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related	The relationship with the use of the protocol- required medication seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the protocol- required medication beyond reasonable doubt when: - the event is a known side effect of the medication category the protocol- required medication belongs to or of similar medication; - the event has a temporal relationship with protocol- required medication use; - the event involves a body-site or organ that o the protocol- required medication are applied to; o the protocol- required medication have an effect on; - the serious event follows a known response pattern to the protocol- required medication (if the response pattern is previously known); - the discontinuation of protocol- required medication use (or reduction of the dose of medication) and reintroduction of its use (or increase of the dose of medication), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of protocol- requiredmedication and the serious event.

18.4Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in Table 18.4-1.

Table 18.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event. • Terminating at the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event at request of medical advisor.	• At request of sponsor.
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 24 hours becoming aware of the event or as per local/regional regulations.

Table 18.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
		• Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event at request of medical advisor.	• At request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event at request of medical advisor.	• When documentation is available • At sponsor request.
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency eCRF with all available new and updated information.	• Within 24 hours of first becoming aware of the event. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event at request of medical advisor.	• At request of sponsor
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. Recommend within 10 business days) after becoming aware of the information • Reporting required through the end of the study • At sponsor request
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event as applicable.	

Abbreviations: AE = adverse event; CRF = case report form; IDE = Investigational Device Exemption; UADE = unanticipated adverse device effect

18.5 Boston Scientific Device Deficiencies

Device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) of study device will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided in Device Management Plan. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency would be recorded as an adverse event on the appropriate eCRF.

18.6 Reporting to Regulatory Authorities / IRBs / ECs / REBs/ Investigators

BSC is responsible for reporting adverse event information and device deficiency to all participating Principal Investigators, IRBs/ECs/REBs, as applicable.

The Principal Investigator is responsible for informing the IRB/EC/REB, and regulatory authorities of UADEs and SAEs as required by local/regional regulations.

According to China local reporting requirements, Boston Scientific Corporation will report all SAEs and device deficiencies that could lead to SAEs to the local regulatory authorities within 5 business days of BSC first becoming aware of the event, and notify all participating investigators/sites and IRBs/ECs in a timely manner.

BSC shall notify all participating study centers if SAEs/SADEs or Device Deficiencies occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs demands changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

19 Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB/EC/REB, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB/EC/REB. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed,

BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB/EC/REB approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC/REB), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC/REB. The new version of the ICF must be approved by the IRB/EC/REB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC/REB. The IRB/EC/REB will determine the subject population to be re-consented.

Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, coronary angiography may demonstrate that the subject is not a

suitable candidate for the trial. A Screening Log will be maintained to document select information about candidates who fail to meet the Comet China trial eligibility criteria, including, but not limited to, the reason for screen failure.

20 Committees

20.1 Safety Monitoring Process

To promote early detection of safety issues, the BSC safety team and its delegated CRO safety team will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information. The BSC Medical Safety group includes physicians with expertise in cardiovascular intervention and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

20.2 Executive Committee

An Executive Committee composed of BSC Clinical Management, study Principal Investigator will be convened. This committee will be responsible for the overall conduct of the study which will include protocol development, study progress, subject safety, overall data quality and integrity, and timely dissemination of study results through appropriate scientific sessions and publications. As appropriate the Executive Committee may request participation of Comet China Investigators on the Committee.

21 Suspension or Termination

21.1 Premature Termination of the Study

Boston Scientific reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

21.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

21.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC /REB Approval

Any investigator, or associated IRB/EC/REB or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

21.3. Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB/EC/REB terminates participation in the study, participating investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

21.4 Criteria for Suspending/Terminating a Study Site

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 6 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

22 Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE;

http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed:

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

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24 Abbreviations and Definitions

24.1 Abbreviations

Abbreviations are shown in Table 24-1.

Table 24-1: Abbreviations

Abbreviation/Acronym	Term
ACC	American College of Cardiology
ACT	Activated clotting time

Abbreviation/Acronym	Term
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
ARC	Academic Research Consortium
ATP	Adenosine-5-triphosphate
BSC	Boston Scientific Corporation
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CK	Creatine Kinase
CK-MB	Creatine Kinase-Myoglobin Band
CRO	Contract Research Organization
eCRF	electronic Case Report Form
CVA	Cerebrovascular Accident
DES	Drug-Eluting Stent
DFU	Directions for Use
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FFR	Fractional Flow Reserve
GCP	Good Clinical Practices
GC	guiding catheters
IC	Intercontinental
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISO	International Standards Organization
ITT	Intention to Treat
LAD	Left Anterior Descending Coronary Artery
LBBB	Left Bundle Branch Block
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction
MLD	Minimum Lumen Diameter

Abbreviation/Acronym	Term
NHLBI	National Heart, Lung, and Blood Institute
NMPA	National Medical Products Administration
PCI	Percutaneous Coronary Intervention
QCA	Quantitative Coronary Angiography
RCA	Right Coronary Artery
RVD	Reference Vessel Diameter
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SCAI	Society for Cardiovascular Angiography and Interventions
STEMI	ST Elevation Myocardial Infarction
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction
TLF	Target Lesion Failure
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
ULN	Upper Limit of Normal

24.2 Definitions

ABRUPT VESSEL CLOSURE

Abrupt vessel closure is the occurrence of new severely reduced flow (TIMI grade 0 or 1) within the target vessel that persists and requires bailout, including emergency surgery, or results in MI or death. Abrupt stent closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt stent closure does not connote “no reflow” due to microvascular flow limitation in which the epicardial artery is patent but has reduced flow. Abrupt stent closure also does not connote transient closure with reduced flow in which the assigned treatment reversed the closure.

Sub-abrupt closure is an abrupt closure that occurs after the target procedure is completed and the subject has left the catheterization laboratory and before hospital discharge.

Threatened abrupt closure is a grade B dissection and ≥50% diameter stenosis or any dissection of grade C or higher.

ARRHYTHMIA

An arrhythmia is any variation from the normal rhythm of the heart, including sinus arrhythmia, premature beats, heart block, atrial or ventricular fibrillation, atrial or ventricular flutter, and atrial or ventricular tachycardia.

BIFURCATION LESION

A bifurcation lesion is a lesion associated with the area where a branch vessel >2.0 mm in diameter by visual estimate originates.

BINARY RESTENOSIS

Binary restenosis is a diameter stenosis >50% at the previously treated lesion site, including the original treated area and the adjacent proximal and distal QCA analysis segment.

BLEEDING CLASSIFICATIONS (*Ref: GUSTO*)

- Severe or life-threatening: Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention
- Moderate: Bleeding that requires blood transfusion but does not result in hemodynamic compromise
- Mild: Bleeding that does not meet criteria for either severe or moderate bleeding

BRAUNWALD CLASSIFICATION OF UNSTABLE ANGINA

Severity

- Class I: New onset, severe or accelerated angina. Subjects with angina of less than 2 months duration, severe or occurring 3 or more times per day, or angina that is distinctly more frequent and precipitated by distinctly less exertion; no pain at rest in the last 2 months.
- Class II: Angina at rest, subacute. Subjects with 1 or more episodes of angina at rest during the preceding month, but not within the preceding 48 hours.
- Class III: Angina at rest, acute. Subjects with 1 or more episodes of angina at rest within the preceding 48 hours.

Clinical Circumstances

- Class A: Secondary unstable angina. A clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia (e.g., anemia, fever, infection, hypotension, tachyarrhythmia, thyrotoxicosis, and hypoxemia secondary to respiratory failure).
- Class B: Primary unstable angina.
- Class C: Postinfarction unstable angina (within 2 weeks of documented MI).

CARDIAC TAMPONADE

Cardiac tamponade is an acute compression of the heart due to effusion of the fluid into the pericardium, or the collection of blood in the pericardium, from rupture of the heart or penetrating trauma.

CARDIOGENIC SHOCK

Cardiogenic shock is a clinical state of hypoperfusion characterized by a systolic blood pressure <80 mmHg and/or a central filling pressure >20 mmHg, or a cardiac index <1.8 liters/min/m^2 where there is evidence of insufficient end organ profusion. Shock is also considered present if intravenous inotropes and/or intra-aortic balloon pump (IABP) are

needed to maintain a systolic blood pressure >80 mmHg and a cardiac index >1.8 liters/minute/m^2.

CREATINE KINASE-MYOGLOBIN BAND

Creatine kinase-myoglobin band (CK-MB) is an isoenzyme of creatine kinase (CK) with a distinct molecular structure specific as an indicator of myocardial cell injury. It is used to evaluate possible causes of chest pain, to detect and diagnose acute MI and re-infarction, and to monitor the severity of myocardial ischemia.

CLINICAL EVENTS COMMITTEE

A CEC is an independent group of individuals with pertinent expertise that review and adjudicate important endpoints and relevant AEs reported by study investigators.

CLINICAL EVENTS COMMITTEE EVENT

The CEC will adjudicate all reported cases of stent thrombosis, TVR, MI (Q-wave and non–Q-wave), and death (to ensure appropriate classification of death as cardiac or non-cardiac). A case adjudicated by the CEC is considered to be a CEC event.

CLINICAL PROCEDURAL SUCCESS (VISUAL ESTIMATE)

Clinical procedural success is post-procedure diameter stenosis <30% in 2 near-orthogonal projections with TIMI 3 flow in all target lesions, as visually assessed by the physician, without the occurrence of in-hospital MI, TVR, or cardiac death.

COMPLICATION (ANGIOGRAPHIC OR CLINICAL)

A complication (angiographic or clinical) is an undesirable clinical event that results in death, injury, or invasive intervention. Complications may include, but are not limited to, perforation, occlusion, intimal flap, dissection, loss of side branch, distal embolization, non-fatal MI, elevated CK Total, prolonged angina, hypotension, hematoma, arrhythmias, etc. Complications may or may not be related to the investigational device.

CONGESTIVE HEART FAILURE

Congestive heart failure is an inadequacy of the heart such that it fails to maintain adequate circulation of blood, so that congestion and edema develop in the tissues. Clinical syndrome is characterized by shortness of breath, non-pitting edema, enlargement of the liver, engorged neck veins, and pulmonary rales.

CORONARY ANEURYSM

A coronary aneurysm is a pathologic dilatation of a segment of a blood vessel involving all three layers of the vessel wall ≥1.5× the RVD.

CORONARY ARTERY SPASM

Coronary artery spasm, or coronary vasospasm, is a spasm of a coronary artery, resulting in a decrease in lumen diameter. It may occur distal to the treatment site and is generally reversed with intracoronary administration of NTG or with adjunct balloon dilatation.

DEATH

Death is categorized as cardiac or non-cardiac.

Cardiac death is defined as death due to any of the following.

- Acute MI
- Cardiac perforation/pericardial tamponade
- Arrhythmia or conduction abnormality
- CVA through hospital discharge or CVA suspected of being related to the procedure
- Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery
- Any death in which a cardiac cause cannot be excluded

Non-cardiac death is defined as a death not due to cardiac causes as defined above.

DISSECTION, NHLBI CLASSIFICATION

- Type A: Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material
- Type B: Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles
- Type C: Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material
- Type D: Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow
- Type E: Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen
- Type F: Filling defect accompanied by total coronary occlusion

DIABETES MELLITUS

Subjects will be categorized as having diabetes mellitus if medical treatment (oral or injection) is required for control of blood glucose levels.

DISTAL EMBOLIZATION

Distal embolization is migration of a filling defect or thrombus to distally occlude the target vessel or one of its branches.

EPICARDIAL VESSEL

Epicardial vessels include the LAD and its branches, the LCX and its branches, and the RCA and its branches.

HYPERTENSION

Hypertension is persistently high arterial blood pressure. Various criteria for its threshold have been suggested, ranging from 140 mmHg systolic and 90 mmHg diastolic to as high as 220 mmHg systolic and 110 mmHg diastolic. Hypertension may have no known cause or be associated with other primary diseases.

HYPOTENSION

Sustained hypotension is a systolic blood pressure less than 80 mmHg lasting more than 30 minutes or requiring intervention (e.g., pacing, IABP, intravenous vasopressors, to sustain systolic blood pressure). This excludes transient hypotension or vagal reactions, which are self-limited or readily reversible.

INDEX PROCEDURE START TIME

Index procedure start time is defined as the time of guide catheter insertion into sheath for the interventional procedure.

INDEX PROCEDURE END TIME

Index procedure end time is defined as the time the guide catheter is removed after the final angiography.

LEFT MAIN DISEASE

Left main disease is a significant lesion in the left main coronary artery of at least 50% diameter stenosis. A protected left main artery means left main with a functioning graft, either venous or arterial, placed to any of the branches of the left main. This is usually the LAD or CX, but could also include one of the branches of those vessels. Having a stent in the left main coronary artery does not in itself constitute a protected left main.

LESION CHARACTERISTICS (ACC/AHA CLASSIFICATION)

- Type A lesions: Minimally complex, length <10 mm, concentric, readily accessible, non-angulated segment (<45°), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, and an absence of thrombus.
- Type B lesions: Moderately complex, tubular (length 10 to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (>45°, <90°), irregular contour, moderate or heavy calcification, total occlusions <3 months old, ostial in location, bifurcation lesions requiring double guidewire, and some thrombus present.
- Type C lesions: Severely complex, diffuse (length ≥20 mm), excessive tortuosity of proximal segment, extremely angulated segments >90°, total occlusions >3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.

LESION LENGTH

Lesion length is measured as distance from the proximal to the distal shoulder in the view that demonstrates the stenosis in its most elongated projection. Lesion length is classified as discrete (<10 mm), tubular (10-20 mm), or diffuse (>20 mm).

LESION LOCATION

Lesion location is the location of the lesion according to the specific coronary artery (i.e., left main, LAD, LCX, or RCA) or bypass graft, and is specified as proximal, mid, or distal. A standard map will be provided to be used for location descriptions.

Note: In this trial, the ramus will be considered to be a branch of the LCX for purposes of determining eligibility and for determining TVR.

LEUKOPENIA

Leukopenia is a leukocyte count of $<3.0 \times 10^9$/liter for more than 3 days.

MALFUNCTION

A malfunction is a failure of the device to meet performance specifications or otherwise perform as intended.

MULTI-VESSEL DISEASE

Multi-vessel disease refers to the presence of >50% diameter stenosis as measured by caliper method or QCA on-line in 2 or 3 major epicardial coronary vessels or bypassed branches.

MYOCARDIAL INFARCTION

In this trial, MI will be defined according to the definition provided below.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy (not for type 2 or 3 MIs).

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*.

Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for *type 2 MI*.

Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.

Criteria for coronary procedure-related myocardial infarction (types 4 and 5 MI)

Percutaneous coronary intervention (PCI) related MI is termed *type 4a MI*.

Coronary artery bypass grafting (CABG) related MI is termed *type 5 MI*.

Coronary procedure-related MI $\leq$ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values $>$ 5 times for *type 4a MI* and $>$ 10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable ($\leq$ 20% variation) or falling, must meet the criteria for a $>$ 5 or $>$ 10 fold increase and manifest a change from the baseline value of $>$ 20%. In addition with at least one of the following:

- New ischaemic ECG changes (this criterion is related to *type 4a MI* only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.

Other types of 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet *type 1 MI* criteria.

Post-mortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.

Criteria for prior or silent/unrecognized myocardial infarction

Any one of the following criteria meets the diagnosis for prior or silent/ unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology.
- Patho-anatomical findings of a prior MI.

PERFORATION

Perforations are classified as follows:

- Angiographic perforation: Perforation detected by clinical site or Angiographic Core Laboratory at any point during the procedure.
- Clinical perforation: Perforation requiring additional treatment, including efforts to seal the perforation or pericardial drainage, or resulting in significant pericardial effusion, abrupt closure, MI, or death.
- Pericardial hemorrhage/tamponade: Perforation causing tamponade.

PSEUDOANEURYSM

A pseudoaneurysm is an encapsulated hematoma in communication with an artery. It is often difficult to distinguish from an expanding hematoma at the site of arterial puncture. It usually requires surgical repair.

REFERENCE DIAMETER OF NORMAL ARTERY SEGMENT

Reference diameter of the normal artery segment is an angiographic measurement of the artery proximal and/or distal to the lesion intended for angioplasty. This is also referred to as "reference vessel diameter" (RVD).

REPEAT INTERVENTION

Repeat intervention is a PCI or CABG performed after the end of the index procedure. The repeat intervention should be performed to improve blood flow.

RESTENOSIS

See Binary Restenosis.

STENT THROMBOSIS (*Ref: Academic Research Consortium Definition)* [31]

Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guide catheter has been removed and the patient left the catheterization lab.

Timing:

- Acute stent thrombosis*: 0-24 hours after stent implantation
- Subacute stent thrombosis*: >24 hours to 30 days after stent implantation
- Late stent thrombosis: >30 days to 1 year after stent implantation

- Very late stent thrombosis: >1 year after stent implantation

* Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis is 0-30 days.

Stent thrombosis may be defined as:

- Confirmed/definite
- Probable
- Possible

Confirmed/Definite (is considered *either* angiographic confirmed or pathologic confirmed)

Angiographic confirmed stent thrombosis is considered to have occurred if:

- TIMI flow is:
  - TIMI flow grade 0 with occlusion originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of thrombus*
  - TIMI flow grade 1, 2 or 3 originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus*

AND at least one of the following criteria, up to 48 hours, has been fulfilled:

- New onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes)
- New ischemic ECG changes suggestive of acute ischemia
- Typical rise and fall in cardiac biomarkers (>2× ULN of CK)

The incidental angiographic documentation of stent occlusion in the absence of clinical syndromes is not considered a confirmed stent thrombosis (silent thrombosis).

* Intracoronary thrombus

Non-occlusive thrombus: Spheric, ovoid or irregular non-calcified filling defect or lucency surrounded by contrast material (on 3 sides of within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

Occlusive thrombus: A TIMI 0 or TIMI 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch).

Probable

Clinical definition of probable stent thrombosis is considered to have occurred in the following cases:

- Any unexplained death within the first 30 days
- Irrespective of the time after the index procedure and MI in the absence of any obvious cause which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis

Possible

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death beyond 30 days.

STROKE/CEREBROVASCULAR ACCIDENT

An acute symptomatic episode of neurological dysfunction attributed to a vascular cause lasting more than 24 hours or lasting 24 hours or less with a brain imaging study or autopsy showing infarction.
Classification:

- Ischemic Stroke: An acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.
- Hemorrhagic Stroke: An acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.
- Undetermined Stroke: A stroke with insufficient information to allow categorization as ischemic or hemorrhagic.

An event that lasts < 24 hours may be adjudicated as a stroke if the following treatments were used:

- Pharmacologic, i.e., thrombolytic drug administration, or
- Non-pharmacologic, i.e., neurointerventional procedure (*e.g.,* intracranial angioplasty)

TARGET LESION

The target lesion is the lesion selected by the Investigator for FFR measurement.

TARGET LESION FAILURE

Target lesion failure is any ischemia-driven revascularization of the target lesion, MI (Q-wave and Non-Q-wave MI) related to the target vessel, or (cardiac) death related to the target vessel. For the purposes of this protocol, if it cannot be determined with certainty whether the MI was related to the target vessel, it will be considered a TLF. if it cannot be determined with certainty whether the Cardiac death was related to the target vessel, it will be considered a TLF.

TARGET LESION REVASCULARIZATION

Target lesion revascularization is any ischemia-driven repeat percutaneous intervention, to improve blood flow, of the successfully treated target lesion or bypass surgery of the target vessel with a graft distally to the successfully treated target lesion. A TLR will be considered as ischemia-driven if the target lesion diameter stenosis is ≥50% by QCA and there is presence of clinical or functional ischemia which cannot be explained by other coronary or graft lesions. Clinical or functional ischemia is any of the following:

- The subject has a positive functional study corresponding to the area served by the target lesion.
- The subject has ischemic ECG changes at rest in a distribution consistent with the target vessel.
- The subject has ischemic symptoms referable to the target lesion.

A TLR will be considered as ischemia-driven if the lesion diameter stenosis is ≥70% by QCA even in the absence of clinical or functional ischemia.

TARGET VESSEL

The target vessel is any coronary vessel (e.g., left main coronary artery, LAD, LCX, or RCA) containing a target lesion. Side branches of a target vessel such as the LAD are also considered part of the target vessel.

TARGET VESSEL FAILURE

Target vessel failure is any ischemia-driven revascularization of the target vessel, MI (Q-wave and non–Q-wave) related to the target vessel or death related to the target vessel. For the purposes of this protocol, if it cannot be determined with certainty whether the MI or death was related to the target vessel, it will be considered a TVF.

TARGET VESSEL REVASCULARIZATION

Target vessel revascularization is defined as a TLR (see definition above) or a TVR remote (see definition below).

TARGET VESSEL REVASCULARIZATION REMOTE

Target vessel revascularization remote is any ischemia-driven repeat percutaneous intervention, to improve blood flow, or bypass surgery of not previously existing lesions diameter stenosis ≥50% by QCA in the target vessel, excluding the target lesion. A TVR will be considered ischemia-driven if the target vessel diameter stenosis is ≥50% by QCA and any of the following are present:

- The subject has a positive functional study corresponding to the area served by the target vessel.
- The subject has ischemic ECG changes at rest in a distribution consistent with the target vessel.
- The subject has ischemic symptoms referable to the target vessel.

A TVR will also be considered as ischemia-driven if the lesion diameter stenosis is ≥70% even in the absence of clinical or functional ischemia.

TECHNICIAN WORKSHEET

A Technician Worksheet is a record for listing the filming sequence and angulations of x-ray equipment, details of inflations, and description of lesion(s).

THROMBUS (ANGIOGRAPHIC)

Thrombus (angiographic) is discrete, mobile intraluminal filling with defined borders with/without associated contrast straining, classified as either absent or present.

THROMBOLYSIS IN MYOCARDIAL INFARCTION CLASSIFICATION

- TIMI 0: No perfusion.
- TIMI 1: Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis of the duration of the cine run.
- TIMI 2: Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel.

- TIMI 3: Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

TOTAL OCCLUSION

A total occlusion is a lesion with no flow (i.e., TIMI flow 0).

Investigator's Declaration

1. *I agree to conduct the trial in accordance with the Declaration of Helsinki, applicable laws and regulations in China, as well as the study protocol.*
2. *I agree to record all data accurately in the Case Report Form (CRF) and to complete the clinical research report within the study timeline.*
3. *I agree to give the sponsor and its designated monitor/auditor and regulatory authorities' representatives consent to monitor, audit and inspect this trial.*
4. *I agree to abide by the clinical research contract /agreement signed by all parties.*

My signature below indicates that I have read and understood the study protocol and the contents above.

Sponsor Signature(stamp) Date

Principal/Coordinating Investigator Signature Date

Institution of clinical trial on medical device Signature Date