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Clinical Investigation Plan Cover Page

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FUSION Clinical Investigation Plan
Validation of OCT-based FUnctional diagnoSIs of corONary stenosis (FUSION)
Study Document No: **ABT-CIP-10331**
Version F
Date: April 14, 2021

Sponsor [redacted]

Abbott

[redacted]

Clinical Investigation Plan

ABT-CIP-10331
FUSION Clinical Investigation Plan
Validation of OCT-based FUnctional diagnoSIs of corONary stenosis (FUSION)

Version Number	[redacted]
Date	April 14, 2021
Study Principal Investigator	[redacted]
Steering Committee	[redacted]
Planned Number of Sites and Region(s)	Up to 30 sites in the United States
Clinical Investigation Type	Prospective, single arm, multi -center, post-marketing study
Abbott Medical Expert	[redacted]
Sponsor	[redacted]
Electronic Data Capture Software	Oracle Clinical Remote Data Capture
OCT and Physiology Core Laboratory	[redacted]
CIP Author of Current Version	[redacted]

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COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki and the applicable regulatory requirements (such as, 21 CFR Part 50, 21 CFR Part 56,21 CFR Part 812, 21 CFR Part 54, and 21 CFR Part 11and 45 CFR part 46). The conduct of the clinical investigation will be approved by the Food and Drug Administration (FDA) and the appropriate Institutional Review Board (IRB) of the respective investigational site.

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1.0 INTRODUCTION

This clinical investigation will be conducted in accordance with this CIP. All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and all study specific training will be documented appropriately.

1.1 Background and Rationale

1.1.1 Background

The Virtual Flow Reserve (VFR) software provides an estimate of Fractional Flow Reserve (FFR) to facilitate the assessment of the hemodynamic significance of coronary lesions imaged by optical coherence tomography (OCT).

[redacted]

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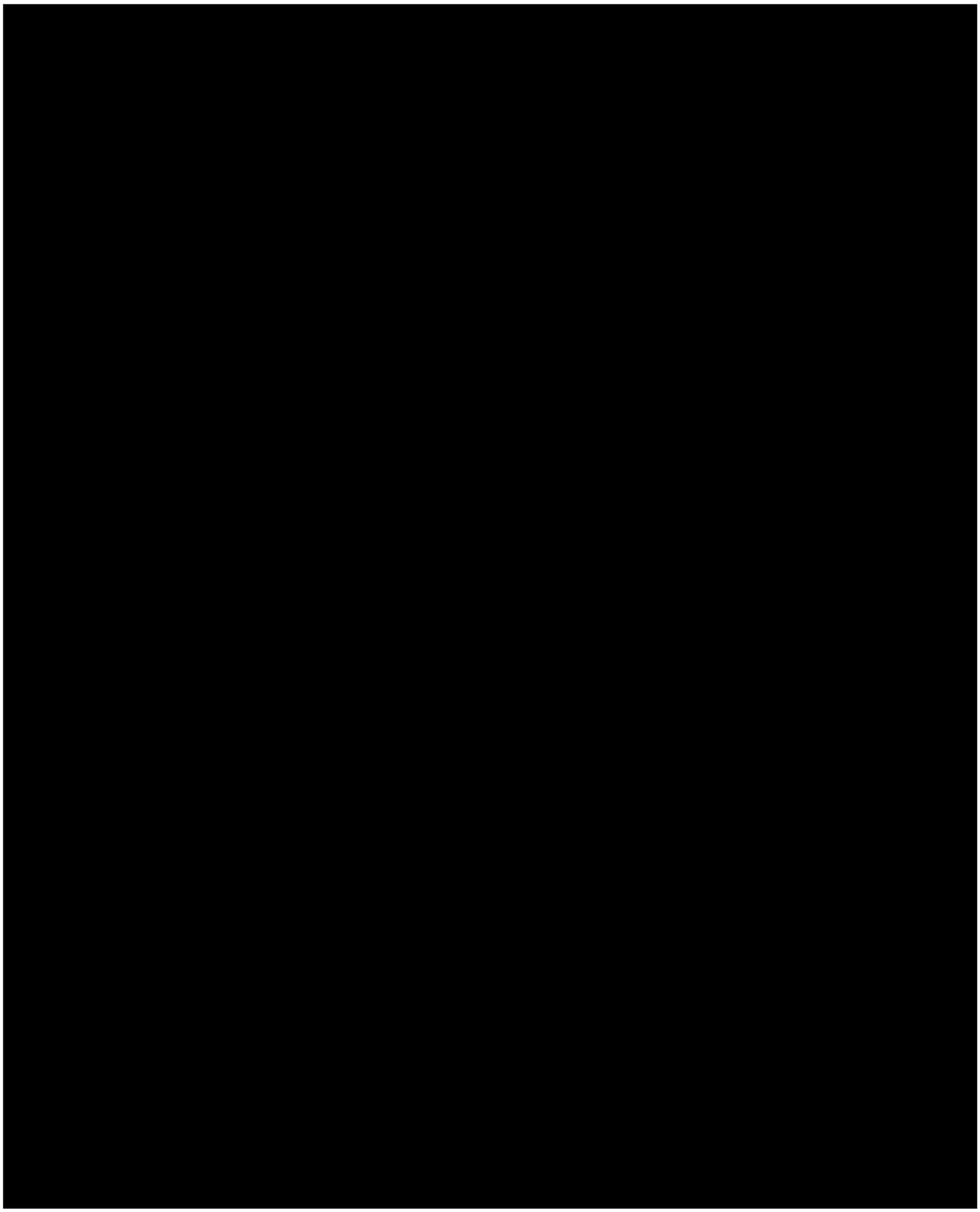

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1.1.2 Rationale for Conducting this Clinical Investigation

FFR has been a useful tool to assess the functional severity of a stenotic lesion in a coronary artery and determine the need for revascularization in many clinical studies (1,2). FFR is the ratio between the pressure distal to the stenosis and the aortic pressure during hyperemia. The predominant advantage of percutaneous coronary intervention (PCI) guidance by coronary physiology is that FFR integrates variables such as luminal narrowing with myocardial perfusion area and collateral flow, leading to a more accurate assessment of myocardial ischemia than coronary angiography alone (1). It has been shown that coronary revascularization can be safely deferred if FFR is above the ischemic threshold of 0.80 (2,3).

The most recent ESC guidelines on myocardial revascularization recommend FFR with the highest degree (Class I, Level of Evidence A) to assess the hemodynamic relevance of intermediate-grade stenosis when evidence of ischemia is not available (4). Pre-PCI FFR has a Class IIa, Level of Evidence B recommendation in Canada, and the US (5). Despite all these recommendations, the adoption rate for FFR remains sub-par, partially due to the use of costly pressure wires and patients' discomfort from the administration of hyperemic agents.

These limitations of FFR may be overcome in part by image-based physiology assessment. For instance, the HeartFlow FFR_{CT} applies computational fluid dynamic (CFD) simulation on CT angiography, which provides a non-invasive coronary fractional flow reserve measurement without a coronary pressure wire or hyperemic agent (6-8). CathWorks FFR_{angio} is derived from routine coronary angiography creating a three-dimensional (3D) reconstruction of the coronary arterial system and estimating the resistance and flow across stenosis (9).

However, FFR_{CT} is limited to a small patient population, given the relatively low penetration of coronary CTA in the US. Additionally, CT imaging technology has significant limitations in the presence of calcified coronary arteries and prior metallic stents (10,11). Furthermore, despite being a non-invasive procedure, both FFR_{CT} and FFR_{angio} may not accurately provide enough detailed vascular morphology compared to intravascular images, which is essential to optimize PCI procedures.

Optical Coherence Tomography (OCT) provides intravascular imaging with high-resolution (10-20 μm) cross-sectional images of plaque morphology, which allows optimizing stent placement and size and strut coverage (12). The results of a recent pilot study[1] suggested that OCT can also be used to characterize the functional severity of the stenotic lesion via an image-based physiology assessment index called Virtual Flow Reserve (VFR). VFR is derived from a flow model based on three-dimensional lumen morphology of the OCT pullback images data to estimate the pre- and post-PCI coronary flow resistance. This technology has the potential to become an important stent planning tool that would be extremely useful to patients with complex lesions if it can be shown to correlate with computational FFR. The present VFR model utilizes a lumped parameter model for deriving the lesion associated physiology based on OCT pullback images. This image-based physiology assessment can not only evaluate the effect of lesion severity on coronary physiology while simultaneously evaluating the vascular/lesion

[1] Document 90465825 Virtual Flow Reserve Tech Report - Data on File at Abbott

condition but can provide the potential for conducting real-time stent planning due to the superior resolution that OCT images provided and the significantly short turnaround calculation time with minimal processing/calculation time.

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

2.1.1 Primary objective

The objective is to validate the diagnostic performance of VFR by comparing it against a reference standard, fractional flow reserve (FFR).

2.2 Device(s) To Be Used in the Clinical Investigation

2.2.1 Name of the Device(s)

The following devices will be used in this clinical investigation:

Device name	Model/Type	Manufacturer	Region/ Country	Investigational or Market Released
ILUMIEN OPTIS OCT Imaging System	C408650	Abbott Laboratories	Global	Market Released
OPTIS Integrated OCT Imaging System	C408652 /C408653	Abbott Laboratories	Global	Market Released
OPTIS Mobile OCT Imaging System	C408661 /C408662	Abbott Laboratories	Global	Market Released
Dragonfly Duo Catheter	C408644 /C408643	Abbott Laboratories	Global	Market Released
Dragonfly OPTIS Catheter	C408645 /C408646	Abbott Laboratories	Global	Market Released
Dragonfly OpStar Catheter	1014651	Abbott Laboratories	Global	Market Released
PressureWire™ X Guidewire Cable Connection (175 cm)	C12009	Abbott Laboratories	Global	Market Released
PressureWire™ X Guidewire Wireless (175 cm)	C12059	Abbott Laboratories	Global	Market Released
PressureWire™ X Guidewire Wireless (300 cm)	C12359	Abbott Laboratories	Global	Market Released

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Please refer to the Instructions for Use (IFU) for details of each respective system.

2.2.2 Indication for Use

Virtual Flow Reserve (VFR) is a physiologic index for diagnosing the functional significance of coronary stenoses based on the vascular morphology information obtained through OCT image pullback. VFR analysis is intended to support the functional evaluation of coronary artery disease and procedural scenario planning. The results of VFR are intended to be used by qualified clinicians in conjunction with the clinical history and symptoms of patients as well as other diagnostic tests according to clinician's professional judgment.

2.2.3 Description of the Device(s)

OPTIS System:

The ILUMIEN OPTIS™, OPTIS™ Integrated, and OPTIS™ Mobile systems with Dragonfly™ DUO or Dragonfly™ OPTIS™ or Dragonfly OpStar™ Imaging Catheter is intended for the imaging of coronary arteries and is indicated in patients who are candidates for transluminal interventional procedures.

The OPTIS™ Systems will further acquire radio frequency signal outputs from both a distal intracoronary pressure transducer and a proximal aortic pressure transducer to determine the physiological parameters, FFR and RFR. The physician may use the FFR and resting full-cycle ratio (RFR) parameter data, along with knowledge of patient history, medical expertise and clinical judgment to determine if therapeutic intervention is indicated.

Dragonfly:

The Dragonfly Duo, Dragonfly OPTIS or Dragonfly OpStar Imaging Catheter with the OCT Imaging System is intended for the imaging of coronary arteries and is indicated in patients who are candidates for transluminal interventional procedures. The Dragonfly Duo, Dragonfly OPTIS or Dragonfly OpStar Imaging Catheter is intended for use in vessels 2.0 to 3.5 mm in diameter. The Dragonfly Duo, Dragonfly OPTIS or Dragonfly OpStar Imaging Catheter is not intended for use in the left main coronary artery or in a target vessel which has undergone a previous bypass procedure.

PressureWire X:

PressureWire™ is designed to be used as a regular guidewire to direct a catheter through the blood vessel and to be used to measure intra-arterial pressures. The PressureWire devices consist of a 0.014" guidewire, a torque device, and a cable hookup, for PressureWire X (cable version), or wireless transmitter, for PressureWire X (wireless version). The guidewire has an integrated sensor chip element located 30 mm from the distal tip to enable measurements of physiological parameters such as pressure. Wireless PressureWire devices are all available in two different lengths, 175 cm and 300 cm. Each PressureWire X (wireless) guidewire is uniquely paired with a transmitter which sends data to a receiver using wireless technology.

PressureWire devices are used primarily for measurement of FFR and RFR. FFR is the ratio between the maximum flow distal to a stenosis and the normal maximum flow in the same vessel, calculated by

FFR = Pd/Pa where Pd is the pressure distal to the stenosis and Pa is the aortic pressure. While FFR is measured during hyperemia, RFR measures Pd and Pa over the entire cardiac cycle at rest (sampled at 100 Hz) and uses a moving average filter to determine the minimum value of the Pd/Pa ratio, which is then averaged over multiple cardiac cycles to obtain the resting index. In case of multiple sequential stenoses or diffuse lesions, RFR pullback pressure assessment can identify multiple lesions with functional significance.

The indications for PressureWire in all geographies can be found in the instructions for use (IFU) provided with the product or on the eIFU.abbottvascular.com website.

Please refer to the IFU for additional information regarding the device used in this clinical investigation.

2.2.4 Summary of Preclinical Studies

A summary of VFR theoretical backgrounds is provided in **Document 90465825 Virtual Flow Reserve Tech Report**[1]

3.0 CLINICAL INVESTIGATION DESIGN

This study is a single-arm, prospective, multi-center study collecting OCT pullback images of lesions pre-PCI and (optional) post-PCI procedure, and the corresponding pressure tracings and physiology indices. No investigational device will be used in this study. VFR will be calculated offline using the OCT pullback images. Up to 30 centers in the US will enroll approximately 310 patients. There will be no clinical follow-up after completion of the PCI procedure. The expected duration of enrollment is approximately 15 months. The total duration of the clinical investigation is expected to be approximately 27 months.

3.1 Clinical Investigation Procedures Schedule

Subjects will be considered enrolled in this clinical investigation when all of the following criteria are met: Informed Consent Form (ICF) is signed, they meet all eligibility criteria and have undergone physiological indices measurement and OCT pullbacks. Enrolled subjects must follow all CIP requirements.

Data will be collected at baseline, during procedure, and post-procedure. There is no clinical follow-up in this study. The flowchart of the process is shown in **Figure 2** below.

[1]Document 90465825 Virtual Flow Reserve Tech Report - Data on File at Abbott

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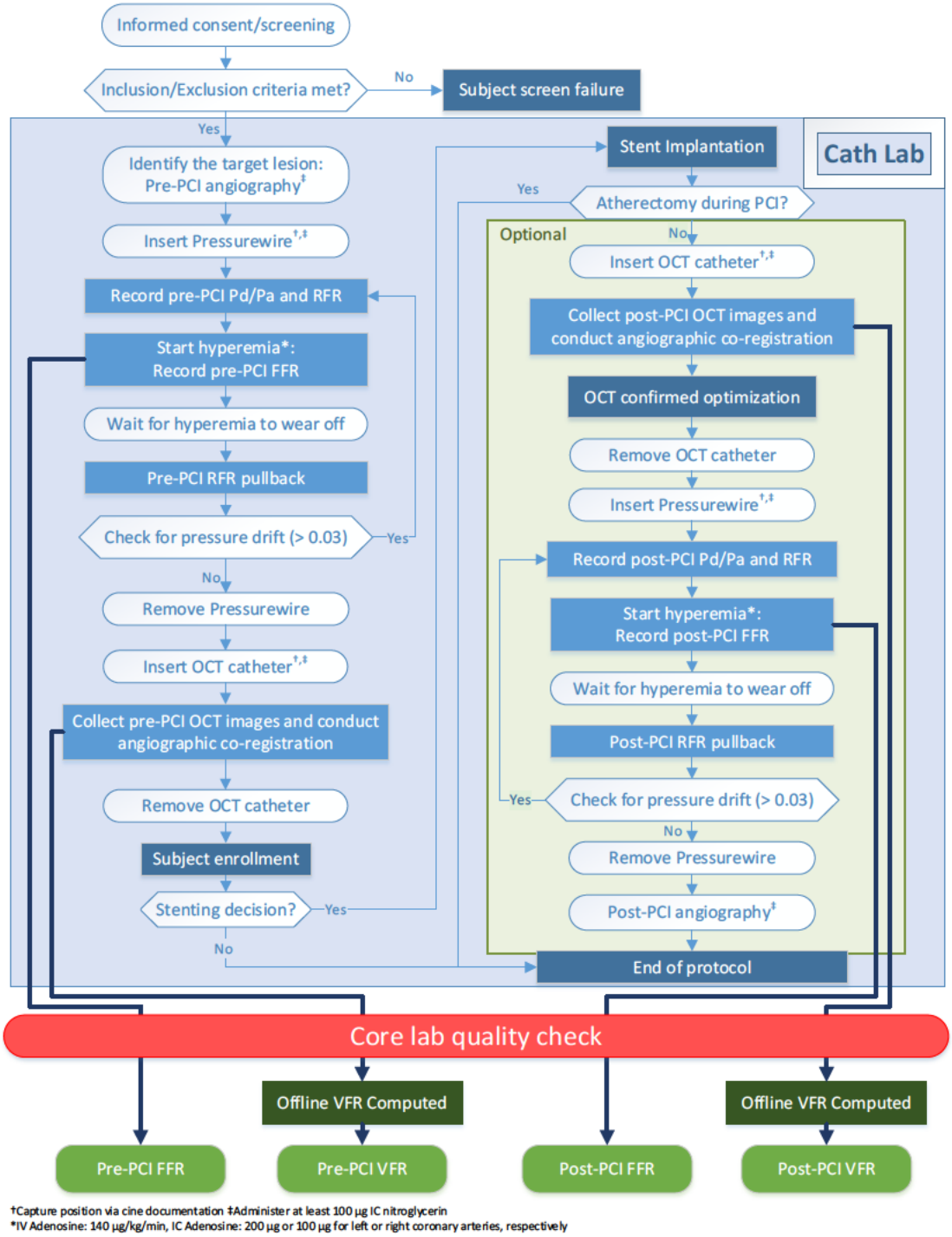
Figure 2: Clinical Investigation Flow Chart



†Capture position via cine documentation ‡Administer at least 100 µg IC nitroglycerin
*IV Adenosine: 140 µg/kg/min, IC Adenosine: 200 µg or 100 µg for left or right coronary arteries, respectively

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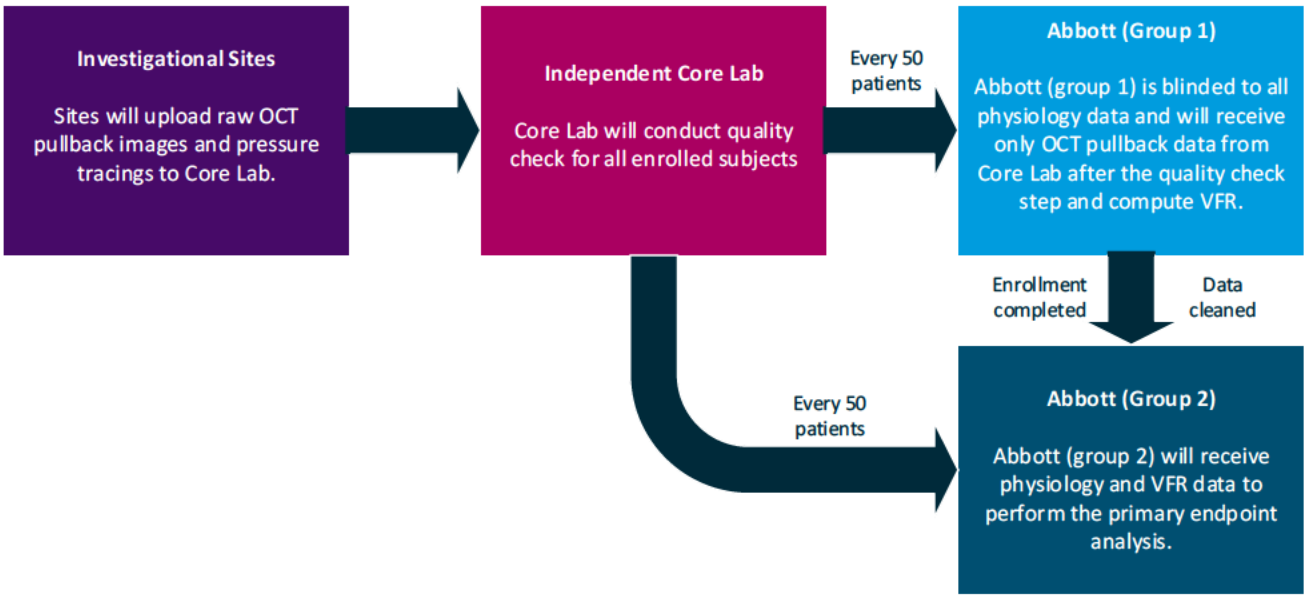
3.2 Measures Taken to Avoid and Minimize Bias

3.2.1 Blinding and Unblinding

Investigational sites will directly upload and transfer the raw unidentified pullback images and pressure tracings to an independent core laboratory. The core laboratory will perform a quality check on OCT pullbacks and pressure tracings. Once the quality check is completed for every 50 patients, these OCT pullbacks will be transferred to Abbott personnel (Group 1) to analyze VFR (**Figure 3**). All Abbott personnel who are responsible for the calculation of VFR (Group 1) will be blinded to all physiology data (Pd/Pa, RFR, and FFR snapshots as well as RFR pullback). Abbott personnel responsible for performing the primary endpoint analysis (Group 2) will be blinded to the VFR data until all patients have been enrolled and all VFR data have been cleaned and generated. Additional data transfer detail is outlined in the data management plan (DMP) document.

Figure 3: Blinding/Unblinding Flowchart



3.2.2 OCT and Physiology Core Laboratory

The clinical investigation will utilize an independent OCT and physiology core laboratory for the assessment and evaluation of all OCT pullbacks and pressure tracings required during the clinical investigation period. All clinical investigation-required OCT pullbacks and pressure tracings must be submitted to the core laboratories by uploading the assessments directly to the core laboratories' database.

Pressure tracings will also be reviewed for pressure drift and significant artifacts per the core laboratory's standard operational procedure. Reasons of rejection for each unacceptable pressure tracing will be documented by the core laboratory. All the remaining acceptable pressure tracings will be subsequently transferred to the sponsor.

To ensure timely feedback on the quality of OCT pullbacks and pressure tracings, as well as a balanced baseline FFR distribution in line with study assumptions, the core lab will send data quality and baseline FFR data to Abbott (group 2) for [redacted] enrolled subjects (**Figure 3**). Based on this information, Abbott may choose to work with the sites on improving data quality as well as rebalancing the FFR distributions via encouraging or capping enrollment in certain subgroup(s). If the enrollment cap is implemented, protocol deviation(s) will be given if the sites do not follow the capping criteria.

3.3 Suspension or Early Termination of the Clinical Investigation

While no formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined, the Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- An oversight committee (e.g., Steering Committee) makes a recommendation to stop or terminate the clinical investigation (such as higher frequency of anticipated adverse device effects)

Should the clinical investigation be discontinued by the Sponsor, subjects will be followed per routine hospital practice with device-related AEs reported to the Sponsor as per vigilance/commercial reporting requirements. The investigator shall provide a written statement to the IRB. All applicable clinical investigation documents shall be subject to the same retention policy as detailed in **Section 11.5** of the CIP.

A Principal Investigator, IRB or regulatory authority may suspend or prematurely terminate participation in the clinical investigation at the investigational site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

4.0 ENDPOINTS

There are two co-primary endpoints and multiple secondary endpoints in this clinical investigation.

4.1 Co-Primary Endpoints and Rationale

The co-primary endpoints of the study will be the sensitivity and specificity of VFR against FFR, each of which will be tested against a prespecified performance goal.

4.2 Secondary Endpoints

Secondary endpoints will be descriptive and will include the overall diagnostic accuracy, positive predictive value (PPV) and negative predictive value (NPV), the correlation between VFR and FFR, and the area under curve (AUC) against FFR.

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll male and female subjects from the general interventional cardiology population. Subjects must meet all eligibility criteria and provide written informed consent prior to conducting any investigation-specific procedures not considered standard of care.

5.2 Subject Screening and Informed Consent

5.2.1 Subject Screening

Potential patients presenting at the clinical sites will be fully informed about the clinical investigation, following the established Informed Consent process (described in **Section 5.2.2**). Once a duly dated and signed Informed Consent form is obtained, the clinical investigation-specific screening procedures may begin.

The following assessments are performed as part of the screening process:

- Clinical indication for angiography with potential for PCI
- Inclusion and exclusion criteria

Subjects must be screened for clinical investigation eligibility by a member of the site's clinical investigation team previously trained to the CIP, and if applicable will be entered into a site-specific screening log.

In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screening failure. The Principal Investigator or the delegated clinical investigation personnel will record the screening failure in the hospital records.

Subjects who signed an Informed Consent form and met general inclusion criteria and no exclusion criteria will participate in the clinical investigation. These patients will also be recorded in the hospital records.

Subject data will be collected following enrollment into the clinical investigation described in **Section 5.4**.

5.2.2 Informed Consent

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's IRB. This process will include a verbal discussion with the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Subjects must be informed about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject's legal rights. Financial incentives will not be given to the subject. Subjects may be compensated for time and travel directly related to the participation in the clinical investigation, if applicable per the Clinical Trial Agreement. The subject shall be provided with the Informed Consent form written in a language that is understandable to the subject and has been approved by the center's IRB. The subject shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the subject understands the information provided. If the subject agrees to participate, the Informed Consent form must be signed and dated by the subject and thereafter by the person obtaining the consent prior to any clinical investigation-specific procedures. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

Failure to obtain informed consent from a subject prior to clinical investigation enrollment should be reported to Sponsor within 5 working days and to the reviewing center's IRB according to the IRB's reporting requirements.

If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee (if applicable) will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing. Enrollment does not occur at the time of signing informed consent.

5.2.2.1 Special Circumstances for Informed Consent

Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority, are excluded from the study population.

The legally acceptable representative will represent the individual during the Informed Consent process, which will be performed according to the requirements in **Section 5.2.2**. The individual will also be informed about the clinical investigation within his/her ability to understand. The explicit wish of the individual to decline participation or withdraw from the clinical investigation at any time will be respected.

Individuals under the age of 18 or age of legal consent are excluded from the study population.

Individuals unable to read or write may be enrolled in this clinical investigation. Informed consent will be obtained through a supervised oral process. An independent witness will be present throughout the Informed Consent process. The written Informed Consent form and any other information will be read aloud and explained to the prospective subject or his/her legally acceptable representative (LAR) and either the subject or LAR will sign and personally date the Informed Consent form. The witness will also sign and personally date the Informed Consent form attesting that the information was accurately explained, and that informed consent was freely given.

Pregnant or breastfeeding women are excluded from the study population.

All other aspects of the Informed Consent process will be in compliance with **Section 5.2.2**.

In addition, an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), must be obtained from the subject or their legally acceptable representative.

For live cases at congresses, the patients need to sign a specific Live Case ICF, approved by the IRB. The investigator must notify the Sponsor prior to performing a live case.

5.3 Eligibility Criteria

5.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. If some of the clinical and laboratory tests are not included in site standard tests, they must be done after written informed consent is obtained. Subjects must meet ALL of the inclusion criteria to be considered for the clinical investigation. If ANY of the exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled. There is no limit on the number of vessels per patient if the vessels met all inclusion and exclusion criteria.

5.3.2 Inclusion Criteria

1. Age ≥18 years
2. Patient provides written informed consent
3. Scheduled for clinically indicated coronary catheterization with the intent to perform physiologic assessment to guide physician clinical course (in lesions with visual % diameter stenosis 40-90%), if clinically indicated
4. Subject is undergoing invasive FFR with Adenosine (high-dose intra-coronary (IC) [200 µg for the left and or 100 µg for the right coronary artery] or 140 µg/kg/min for intravenous (IV)) used as hyperemic stimulus
5. Clinical presentation with or history of stable angina, unstable angina, or silent ischemia (defined as abnormal stress test or abnormal invasive physiology assessment) that has led to the procedure

5.3.3 General Exclusion Criteria

1. Prior history of myocardial infarction (MI) in the target vessel
2. Presence of acute ST Elevation Myocardial Infarction (STEMI)
3. Culprit vessel of Non-ST Elevation Myocardial Infarction (NSTEMI)
4. TIMI flow < Grade 3 at baseline or visible thrombus
5. Prior history of coronary artery bypass grafting (CABG)
6. Prior heart transplant
7. Severe valvular heart disease or history of valve repair or replacement
8. Prior history of PCI with stent in target vessel, or target vessel involves in-stent restenosis
9. Target coronary vessel is supplied by major collaterals or is supplying major collaterals to a CTO (chronic total occlusion)
10. CTO in the target vessel
11. Severe diffuse disease observed in target vessel defined as the presence of diffuse, serial

gross luminal irregularities present in the majority of the coronary tree
12. Presence of any myocardial bridge (MB), regardless of vessel location
13. Contraindication for FFR examination or administration of vasodilators
14. Known LVEF ≤45%
15. Target lesion involves Left Main coronary artery or ostial right coronary artery
16. Known renal insufficiency (eGFR < 30 ml/kg/m^2 or serum creatinine ≥ 2.5 mg/dL) unless patient is on dialysis
17. Heart Failure NYHA Class III or IV
18. Subject is pregnant (For a female subject of childbearing potential, a pregnancy test must be performed within 14 days (≤14 days) prior to the index procedure per site standard test)
19. Subject has or had active COVID-19 symptoms and/or a positive test result within the prior 2 months
20. Participation in another clinical study of an investigational drug or device
21. Presence of aneurysm in the target vessel

5.3.4 Imaging and Pressure Tracing Exclusion Criteria

1. Artifact in pre-PCI OCT for the target lesion or in the event of multiple target lesions, artifact in pre-PCI OCT for ALL target lesions
2. Target lesion requires any preparation (including but not limited to balloon dilatation, atherectomy, etc.) prior to pre-PCI OCT and physiology measurements, or in case of multiple target lesions, ALL target lesions require any preparation (including but not limited to balloon dilatation, atherectomy, etc.) prior to pre-PCI OCT and physiology measurement
3. Severe vessel tortuosity or calcification in the target vessel such that it is unlikely that the OCT catheter can be delivered
4. Target lesion not imaged by OCT or in the event of multiple target lesions, ALL target lesions not imaged by OCT
5. Pressure drift of > 0.03; i.e. Pd and Pa ratio value < 0.97 or > 1.03, unless physiology measurements are repeated after re-equalization
6. Target lesion or significant CAD beyond 60 mm from coronary ostium; i.e. not able to clearly image and capture all disease segment with OCT in 1 run
7. Incorrectly done or unsuccessful catheter purge and/or contrast flush
8. Presence of plaque rupture and/or intravascular hematoma in target vessel (visual % diameter stenosis ≥ 40%)
9. Inability to receive intracoronary nitroglycerin prior to OCT or FFR
10. Use of flush media other than radiographic contrast

5.4 Subject Enrollment

Subjects are considered enrolled in this clinical investigation after signing the ICF, met all inclusion criteria and has undergone physiological indices measurement and OCT pullbacks. If ANY of the exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled.

If subjects are enrolled into the clinical investigation and are later found to have met exclusion criteria or not all inclusion criteria, these subjects will be included in the analysis population and must follow all the

CIP requirements. Enrolled subjects may be excluded from the analysis population due to the quality check by core laboratory based on OCT pullback and pressure tracing data.

5.4.1 Enrollment of Medicare Beneficiaries

This clinical investigation will enroll Medicare beneficiaries and therefore conforms to all standards of Medicare coverage requirements. The Risks and Benefits section describes how all enrolled subjects, including Medicare beneficiaries, may be affected by the device under investigation.

Subjects enrolled in the clinical investigation are expected to be consistent with the Medicare population based on age and as such, the clinical investigation results are expected to be generalizable to the Medicare population.

5.4.2 Historically Under-Represented Demographic Subgroups

The Sponsor intends to implement FDA's guidance on sex-specific data in medical device clinical investigations to ensure adequate representation of women and other traditionally under-represented demographic subgroups in this clinical investigation. As noted in the guidance, some barriers to participation of women and ethnic minorities in clinical investigations have traditionally been:

- Lack of understanding about main obstacles to participation of such subgroups in clinical research
- Inclusion/exclusion criteria potentially not needed to define the clinical investigation population may unintentionally exclude specific subgroups
- Under diagnosis of disease etiologies and pathophysiology leading to under referral of demographic subgroups
- Avoidance of specific subgroups by investigators and Sponsors due to the perception that it takes more time and resources to recruit them
- Fear of fetal consequences (for female participants)
- Family responsibilities limiting women's ability to commit time for follow-up requirements

The Sponsor will take the following steps to ensure adequate representation of women and racial or ethnic minorities in this clinical investigation:

- The Sponsor will provide training to investigational site personnel to ensure adequate representation of these demographic subgroups
- The Sponsor will approach sites without bias or consideration for specific demographic subgroups

5.5 Subject Discontinuation

Each enrolled subject shall remain in the clinical investigation until completion of index procedure; however, a subject's participation in any clinical investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject withdrawn by the Investigator

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to their respective IRB as defined by their institution's procedure(s).

5.6 Number of Subjects

The clinical investigation will enroll approximately 310 subjects.

5.7 Total Expected Duration of the Clinical Investigation

The total duration for the clinical investigation, including subject recruitment, data collection and clinical investigation closure, is expected to be up to 27 months.

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Baseline/Pre-procedure/Pre-treatment

The site Principal Investigator is responsible for ensuring all clinical investigation data is collected as required per CIP scheduled procedures.

6.1.1 Baseline Assessments

All baseline tests will be done within 30 days prior to the index procedure, unless otherwise specified by the protocol.

- Demographics: include subject's age and sex
- Cardiovascular history (most recent values closest to baseline visit)
- Medical history: indicate subject's risk factors, relevant co-morbidities, previous cardiac procedures
- Medication (only chronic medication): indicate the drug category the subject is currently taking on a long-term basis, i.e. no short-term medication
- Serum creatinine, hematocrit, and hemoglobin measured
- LVEF assessment (if no LVEF test result within 3 months is available). Assessment can be by echocardiography, multiple gated acquisition (MUGA), magnetic resonance imaging (MRI), ventriculography (LV gram) or other method
- CHF assessment (NYHA class)
- Physical examination: include subject's height, weight (measurements taken during visit)
- 12-lead ECG
- Negative pregnancy test is required for any female of childbearing potential within 14 days prior to index procedure

- Angiogram Imaging - Diameter Stenosis (%)

6.1.2 Baseline and Post-PCI Imaging Assessments

Coronary angiography is an invasive test where radiopaque dye is injected through a catheter into the coronary arteries to assess severity of narrowing(s) from coronary artery disease.

Following administration of at least 100 µg IC nitroglycerin, angiography of the lesion should be performed in at least 2 contralateral **views without panning** for both baseline and (optional) post-PCI.

6.1.3 Pre-procedure CIP-Required Medications

Patients shall receive medication prior and post-PCI per standard of care.

6.2 PCI Procedure

The following is a description of the image acquisition and treatment steps to be used during the index procedure. The pre-PCI procedures should be conducted in the following order: Pd/Pa and RFR snapshot measurement, FFR measurement, dedicated period for resolution of hyperemia, RFR pullback measurement, drift check, and OCT imaging procedure. The optional post-PCI step should include final OCT imaging procedure, followed by physiological measurements (refer to the flowchart in **Figure 2**). Post-PCI study data collection step is optional but strongly recommended if PCI is performed.

All OCT data and physiological indices measurements will be stored digitally for subsequent analysis and these images must be sent to the Core Laboratory for quality check.

Any vessel preparation (if necessary) with balloon dilation or atherectomy should be performed only after pre-PCI physiological indices measurement and OCT have been performed.

If applicable, PCI will be performed according to local standard practice. PCI information will be collected on the appropriate eCRF. For each treated lesion, the guiding catheter size, the total number of stents used, and the relevant stent information (diameter and length) must be recorded on the appropriate eCRF. Any vessel preparation step including, pre-dilation, post-dilation, or atherectomy device use must also be recorded. If the subject undergoes atherectomy during PCI, post-PCI OCT and physiological steps are not needed and that is the end of the protocol for the subject.

6.2.1 Physiological indices measurement procedures

In all cases, physiological indices measurement must be performed. Any standard guidewire must be removed completely from target vessel prior to any physiological measurement.

At least 100 µg IC nitroglycerin must be administered prior to physiological assessment. The preparation and use of the PressureWire will be according to its respective IFU. The aortic pressure transducer and PressureWire must both be equilibrated to zero pressure outside of the body. The PressureWire is then advanced to the aorto-ostial junction where PressureWire equalization is performed after ensuring the presence of an appropriate aortic waveform (distinct dicrotic notch), with guide disengagement performed, if necessary. PressureWire is then advanced across the lesions with the sensor positioned into the distal coronary artery and at least 10 mm distal to the most distal target lesion. The PressureWire position is then captured via cine documentation with contrast administration (this may be successfully

achieved by capturing the image during saline flush of residual contrast within the guiding catheter), and baseline pressures documented prior to inducing hyperemia following confirmation of an appropriate aortic waveform (distinct dicrotic notch), with guide disengagement, if necessary. Pre-PCI and (optional) post-PCI Pd/Pa and RFR snapshot values and tracings will be collected.

For FFR measurement, maximal hyperemia is induced per standard practice (140 µg/kg/min IV or high dose 200 µg or 100 µg for the left or right coronary artery IC adenosine, respectively) and recorded until a stable minimum FFR reading has been achieved. FFR values and tracings, will be recorded and captured for both pre-and (optional) post-PCI.

Following successful Pd/Pa, RFR, and FFR measurements and once resting conditions have been re-established (minimum wait 1 minute after IC administration and 3 minutes following IV administration), a slow and measured RFR pullback is conducted both pre-PCI and (optional) post-PCI. At the end of the both pre-PCI and (optional) post-PCI RFR pullback, a drift check should be performed, and a snapshot of the end value of Pd/Pa in FFR mode needs to be recorded.

6.2.2 OCT procedures

The preparation and use of the OCT catheter will be according to its respective IFU. For all indicated vessels, if less than 10 minutes have passed since the last dose of IC nitroglycerine, no extra dose is needed. If more than 10 minutes have passed since the last dose of IC nitroglycerine, at least 100 µg IC nitroglycerin should be re-administered before OCT pullbacks. The proximal and distal reference segments are initially identified by angiography. The proximal and distal reference diameters should be recorded on the eCRF. OCT Imaging must be performed using the pullback device at 75 mm pullback (survey mode), 5 frames per mm over 2.1 seconds. The OCT catheter should be placed at the location where the imaging lens is at the same location as the PressureWire sensor and would reach the guide catheter at the end of the imaging run as well as at least 10 mm distal to the distal end of the lesion, with the aim of imaging as much of the coronary artery as possible. All significant lesions in a vessel need to be within a single OCT pullback. OCT pullback image will be qualified as long as all disease segment was captured. The lens position should be captured via cine documentation prior to each pullback. For standard pullback, the recommended contrast injection volume is 14 ml at an injection rate of 4 mL/s in the left coronary artery and 12 mL at an injection rate of 3 mL/s in the right coronary artery. Cine angiography with contrast opacification of the coronary artery in the desired angiographic co-registration view(s) must be performed during the pre- and (optional) post-PCI OCT pullback without panning. Contrast volume and method are collected on the eCRF.

For cases with PCI, the post-PCI study data collection step is optional. If a post-PCI study data collection was performed, both intermediate and final OCT pullbacks should be collected after OCT-guided stent optimization was done, and the post-PCI physiological assessment must be performed after the final OCT run. Pre-PCI, (optional) intermediate post-PCI, and (optional) final post-PCI OCT pullback images need to be uploaded to the OCT Core Laboratory via BioClinica website.

6.2.3 Multiple target lesions/vessels treatment

Subjects requiring multi-vessel PCI may be enrolled in this trial. There is no limit on the number of target lesions per epicardial vessel and target vessels per patient in this study. All target lesions and vessels must satisfy all inclusion and exclusion criteria.

6.2.4 Non-target lesion/vessel treatment

Non-target lesion/vessel treatment (i.e., lesion/vessel that does not meet the inclusion/exclusion criteria) are not allowed prior to or during the study-required procedure. They may be treated either after the study-required procedure is completed within the same PCI procedure or as a staged procedure. In either case, the study participation will end at the completion of the study-required procedure (during the index procedure).

6.2.5 Staged procedure considerations

All aspects of the study protocol must occur during one procedure, which is considered the study index procedure. This may be a planned staged procedure based on a diagnostic catheterization (pre-or post-consent). Subject participation begins at the index procedure upon study device insertion in enrolled subjects. The enrollment is based on subjects satisfying all eligibility criteria and had a successful pre-PCI physiological indices measurement and OCT imaging conducted on the qualified lesion(s)/vessel(s). Subject participation ends at the conclusion of the study index procedure with or without PCI performed. There will be no data collection from any additional staged procedure as subject participation ends at the conclusion of the study index procedure and the subject cannot be re-enrolled in the study.

6.2.6 Bifurcation lesions consideration

Bifurcation lesions consideration is shown in **Figure 4**.

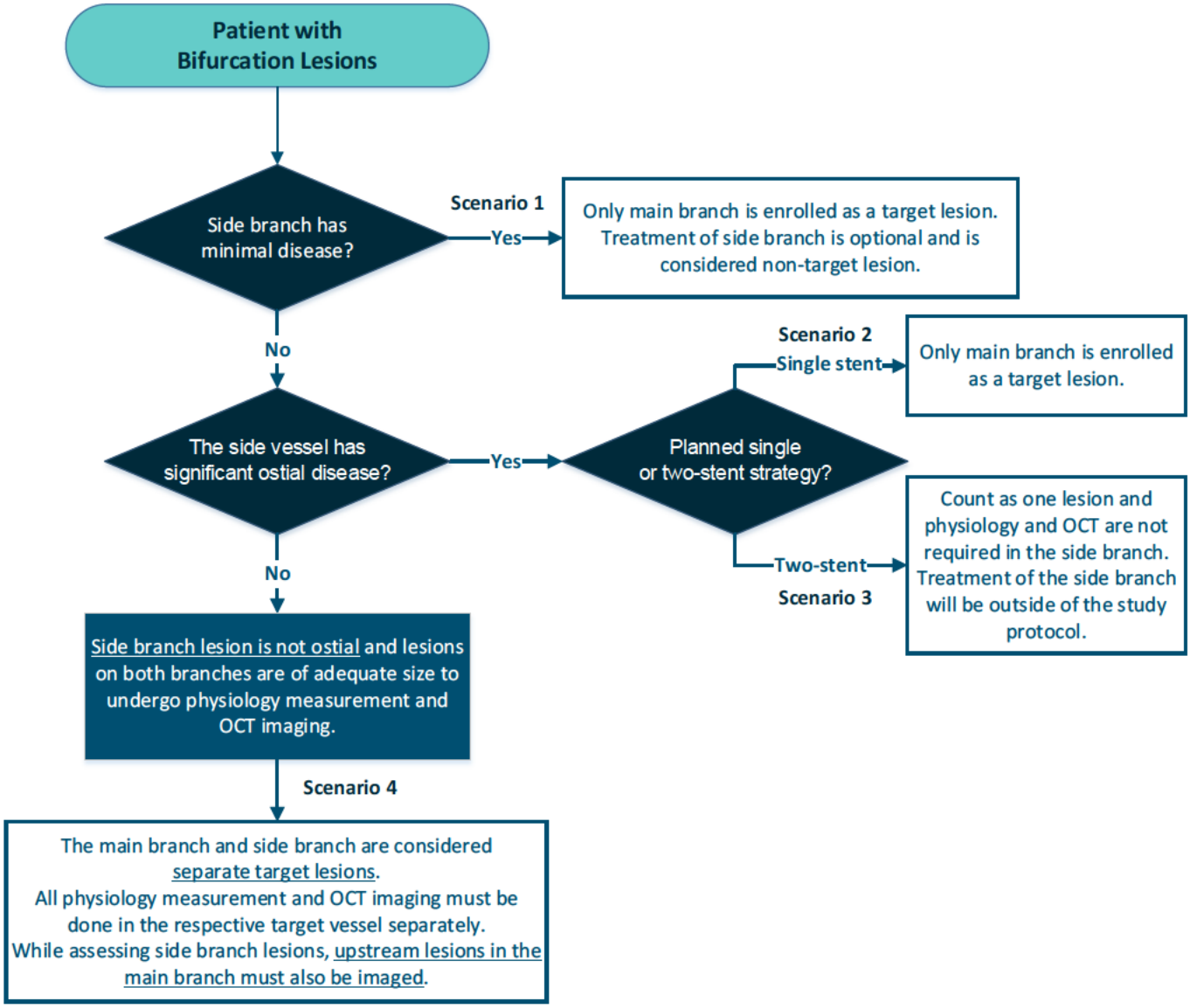
- **Scenario 1**: For the main branch lesion with a side branch that has a minimal disease which is defined as <40% diameter stenosis by visual estimate), the main branch lesion can be enrolled as the target lesion. Treatment of the side branch is optional and outside of the study protocol.

- **Scenarios 2 and 3**: If the side branch vessel has significant ostial disease with a planned single (**Scenario 2**) or two-stent (**Scenario 3**) strategy, only the main vessel can be enrolled into the study, following the FUSION workflow in the main branch. For two-stent strategy, this will count as one lesion and physiology measurement and OCT imaging are not required in the side branch. Treatment of the side branch will be outside of the study protocol.

- **Scenario 4**: For the main branch and side branch lesions that are both to be considered as target lesions, these two lesions need to be distant from each other (i.e., side branch lesion is not ostial) treated independently and both branches are of adequate size to undergo physiology and OCT measurements. In that setting, the main and the side branch are considered separate target vessels and all physiology and OCT. The measurements of both physiology and OCT must be done in the respective target vessel separately. i.e., in the side branch for the side branch lesion assessment. Of note, while assessing side branch lesions, upstream lesions in the main branch must also be imaged.

Clinical Investigation Plan

Figure 4: Bifurcation Lesions Consideration



6.3 Post–PCI (In-hospital)

The timing and method of vascular sheath removal, as well as timing of ambulation, use of post-procedural medications and discharge is per standard of care. Study participation ends when the subject leaves the catheterization laboratory.

6.4 Follow-up Assessments

No follow-up will be required in this study.

6.5 Additional Information on Required Assessments

Physical Examination

Physical examination will be completed and recorded at baseline. Any clinically significant findings during the physical examination should be reviewed by the investigator. Any clinically significant findings during the baseline physical examination should be reported in the subject medical history. Any clinically significant findings during physical examinations post-device insertion should be reported as adverse events. Physical examinations should be performed per the standard of care and may be completed by any qualified medical personnel.

6.5.1 Schedule of Events

CIP Activity	Enrollment	Baseline (within 30 days otherwise stated in the CIP)	Procedure
Informed Consent Process	X		
Demographics and Medical History		X	
Physical Exam		X	
Pregnancy Test [1]		X	
LVEF		X	
NYHA Assessment		(X)	
12 Lead ECG		X	
Serum Creatinine		X	
Hematocrit		X	
Hemoglobin		X	
Pre-PCI Angiography		X	
Pre-PCI Physiological Indices			X
Pre-PCI OCT			X
Pre-PCI Angiographic Co-registration			X
PCI			(X)
Post-PCI OCT			(X)[2]
Post-PCI Angiographic Co-registration			(X)[2]
Post-PCI Physiological Indices			(X)[2]
Post-PCI Angiography			(X)[2]
Cardiac Medications		X	
Adverse Event			X

[1]For women of childbearing potential
[2]Optional

6.6 Physiology and OCT Core Laboratories

This clinical investigation will utilize an independent core laboratory for the assessment and evaluation of all pre-and post-PCI OCT pullback images and corresponding pressure recordings required during the clinical investigation period.

All clinical investigation-required pre-and post-PCI OCT pullback images and corresponding pressure recordings should be submitted to the core laboratories by uploading the assessments directly to the core laboratory's database. The core laboratory will review and provide quality check of all pullback images and pressure tracings.

The core laboratory will review co-registered angiography and OCT pullbacks, and exclude cases with spastic artery, myocardial bridge and accordion effect. After successful auto-calibration of OCT pullback, the core laboratory will exclude cases with low image quality caused by significant blood in lumen or catheter purge issue as well as cases that present with OCT artifact. The core laboratory will reject pullback with the presence of ruptured plaques, hematoma, thrombus or old stent.

Pressure tracings will also be reviewed for pressure drift and significant artifacts per the core laboratory's standard operational procedure, and reasons of rejection for each unacceptable pressure tracing will be documented by the core laboratory.

All the remaining acceptable OCT pullback images and pressure tracings will be used for endpoint analysis. VFR computed using Abbott validated software will be validated against the core lab reported FFR.

7.0 ADVERSE EVENTS

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1 Definition

7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under investigation.

Note 1: This definition includes events related to the medical device under investigation or the 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 medical devices under investigation.

7.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death,

b) Led to a serious deterioration in health of the subject, that either resulted in

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.
5. chronic disease

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

7.1.3 Device Deficiency/Device Malfunction

Device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Note: Performance specifications include all claims made in the labeling of the device.

A device malfunction is the failure of a device to meet its performance specifications or otherwise perform as intended, when used in accordance with the instructions for use or CIP.

7.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

7.3 Adverse Event and Device Deficiency/Device Malfunction Reporting

7.3.1 Adverse Event Reporting

General AE Reporting

Safety surveillance and reporting will be done only for enrolled subjects, and it starts when the study device is introduced into the subject's vasculature. Safety surveillance and reporting will continue through

the procedure and end when the subject has left the procedure room, the subject is deceased, the subject concludes participation in the clinical investigation, or the subject withdraws from the clinical investigation, whichever occurs first. Adverse events will not be collected for screen failure subjects. All adverse event data, including deaths and device deficiency data (if applicable), will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information with regard to an adverse event should be updated within the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

An offline form will be made available to allow the investigator to report SAEs in the event the entry cannot be made in the EDC. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

Non-cardiac related abnormal laboratory values will not be considered AEs unless:

1. the investigator determined that the value is clinically significant,
2. the abnormal lab value required intervention, or
3. the abnormal lab value required subject withdrawal from the clinical investigation.

All adverse events will be collected on each subject through the end of the procedure.

SAE Reporting

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

7.3.2 Device Deficiency/Malfunction Reporting

All device deficiencies/malfunctions should be reported on the appropriate CRF form.

The investigator should report all device deficiencies/malfunctions to the Sponsor as soon as possible but no later than outlined below.

Clinical Sites	Reporting timelines

All Sites	Device deficiencies/malfunctions must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The device should be returned to the Sponsor.

Device deficiencies/malfunctions should be reported to the IRB per the investigative site's local requirements.

An offline form will be made available to allow the investigator to report device deficiencies/malfunctions in the event that the entry cannot be made in the EDC system. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

In case a device deficiency/malfunction occurred before the patient ID has been assigned, the device deficiency should be reported to the Sponsor via the offline reporting form.

7.3.3 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs and reportable device deficiencies/malfunctions to the country regulatory authority, per local requirements.

Note: Reportable device deficiencies/malfunctions include device deficiencies/malfunctions that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. Additional details on statistical analyses, including justification of clinical investigation design, sensitivity analyses, poolability analyses, subgroup analyses and analysis of descriptive endpoints, may be maintained in a separate Statistical Analysis Plan (SAP).

8.1 Analysis Populations

The primary analysis population will include all subjects who have signed informed consent, met all inclusion and exclusion criteria, and have acceptable OCT pullbacks and pressure tracings for computing both the VFR and FFR indices

8.2 Statistical Analyses

8.2.1 Primary Endpoint(s) Analyses

The co-primary endpoints of the study will be the sensitivity and specificity of VFR against FFR, each of which will be tested against a prespecified performance goal.

FFR with a binary cut-off of 0.80 will be used as the reference standard for comparison, and an FFR value ≤ 0.80 will be considered positive (ischemia-causing) and an FFR value > 0.80 will be considered negative (non-ischemia-causing).

Similarly, a VFR value ≤ 0.80 will be considered positive (ischemia-causing) and a VFR value > 0.80 will be considered negative (non-ischemia-causing).

The following 2x2 table provides diagnostic definitions of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) within the context of this study.

	FFR ≤ 0.80	**FFR > 0.80**
VFR ≤ 0.80	True Positive (TP)	False Positive (FP)
VFR > 0.80	False Negative (FN)	True Negative (TN)

The following sections contain these diagnostic definitions of TP, FP, FN, and TN to explain how to calculate the endpoint data.

8.2.1.1 Primary Endpoint: Overall Sensitivity

The first co-primary endpoint is the overall sensitivity of VFR against FFR.

8.2.1.1.1 Hypothesis

[redacted]

8.2.1.1.2 Analysis Method

The overall sensitivity of the hybrid approach will be estimated using the 2×2 contingency table comparing VFR and FFR measurements. Sensitivity is defined as the proportion of VFR positive lesions(13), in the group of FFR positive lesions, which can be expressed in the following way:

$$Sensitivity = \frac{TP}{TP + FN}$$

Where TP denotes the number of True Positives (both VFR and FFR positive) and FN denotes the number of False Negatives (VFR negative but FFR positive).

[redacted]

8.2.1.2 Primary Endpoint: Overall Specificity

The second co-primary endpoint is the overall specificity of VFR against FFR.

8.2.1.2.1 Hypothesis

[redacted]

8.2.1.2.2 Analysis Method

The overall specificity of the hybrid approach will be estimated using the 2×2 contingency table comparing VFR and FFR measurements. Specificity is defined as the proportion of VFR negative lesions in the group of FFR negative lesions(13), which can be expressed in the following way:

$$Specificity = \frac{TN}{TN + FP}$$

Where TN denotes the number of True Negatives (both VFR and FFR negatives) and FP denotes the number of False Positives (VFR positive but FFR negative).

[redacted]

8.2.2 Secondary Endpoint(s) Analyses

Secondary endpoints will be descriptive and will include the overall diagnostic accuracy, the positive predictive value (PPV), the negative predictive value (NPV), the correlation between VFR and FFR, and the area under curve (AUC) against FFR will also be descriptively analyzed.

8.2.2.1 Secondary Endpoint #1: Overall diagnostic accuracy

The overall diagnostic accuracy will be estimated using the 2×2 contingency table comparing VFR and FFR measurements. Overall diagnostic accuracy is defined as the proportion of correctly classified lesions among all lesions (13), which can be expressed in the following way using the definition:

$$Overall\ Diagnostic\ Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

Where TP denotes the number of True Positives, FN denotes the number of False Negatives, TN denotes the number of True Negatives, and FN denotes the number of False Negatives.

The point estimate and 95% confidence interval for this statistic will be reported.

8.2.2.2 Secondary Endpoint #2: Positive predictive value (PPV)

PPV will be estimated using the 2×2 contingency table comparing VFR and FFR measurements. PPV is defined as the proportion of lesions with the disease and with a positive test result among the group of lesions with a positive test result(13), which can be expressed in the following way using the definition:

$$PPV = \frac{TP}{TP + FP}$$

Where TP denotes the number of True Positives and FP denotes the number of False Positives.

The point estimate and 95% confidence interval for this statistic will be reported.

8.2.2.3 Secondary Endpoint #3: Negative predictive value (NPV)

NPV will be estimated using the 2×2 contingency table comparing VFR and FFR measurements. NPV is defined as the proportion of lesions without the disease and with a negative test result among the group of lesions with negative test results(13), which can be expressed in the following way using the definition:

$$NPV = \frac{TN}{TN + FN}$$

Where TN denotes the number of True Negatives and FN denotes the number of False Negatives.

The point estimate and 95% confidence interval for this statistic will be reported.

8.2.2.4 Secondary Endpoint #4: Correlation between VFR and FFR

The correlation between VFR and FFR will be estimated as the R^2 correlation coefficient from the simple linear regression model using VFR value as the independent variable and FFR as the dependent variable. The point estimate and 95% confidence interval for this statistic will be reported.

8.2.2.5 Secondary Endpoint #5: Area under curve (AUC) against FFR

AUC will be estimated as the area under the ROC curve. To construct a ROC curve, we plot 1-specificity on the x-axis and sensitivity on the y-axis (13) . Sensitivity and specificity are calculated at various values of VFR and FFR, and the AUC curve will be drawn using logistic regression. The point estimate and 95% confidence interval for this statistic will be reported.

8.3 Sample Size Calculation and Assumptions

[redacted]

[1] Fearon WF eta al. Accuracy of Fractional Flow Reserve Derived from Coronary Angiography. Circulation Vol 139 (4): 477-484
[2] Document 90465825 Virtual Flow Reserve Tech Report - Data on File at Abbott
[3] Internal RFR Technology Development Document - Data on File at Abbott

8.4 Timing of Analysis

The primary endpoint analysis will be conducted after 310 subjects have undergone a procedure and usable VFR and FFR readings have been obtained.

8.5 Subgroup Analysis

Subgroups to be analyzed will be outlined in the SAP.

8.6 Multiplicity

Since the endpoints are co-primary and both must be passed to declare study success, there is no need for multiple comparison adjustment.

8.7 Pooling Strategy

All pullback images and pressure tracings from different sites will be pooled for this validation study. Details of the pooling strategy will be described in the SAP

8.8 Procedures for Accounting for Missing Data

Details regarding the treatment of missing, unused, or spurious data, including missing data due to subject drop-out, early withdrawal, exclusion of particular information from the testing of the hypothesis, and lost-to-follow-up may be provided in the SAP.

8.9 Planned Interim Analysis

No interim analysis is planned for this study.

8.10 Statistical Criteria for Termination

There are no statistical criteria for termination of this clinical investigation.

8.11 Success Criteria

The clinical investigation will be deemed a success if both primary endpoint hypotheses are rejected at the 0.025 level.

8.12 Deviations from Statistical Plan

Any major changes to the statistical plan will be documented in an amendment to the statistical plan. Less significant changes to the planned analyses will be documented in the final report.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for the purpose of performing clinical investigation-related monitoring, audits, IRB/EC review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities including foreign countries to review, in confidence, any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however, Sponsor undertakes not to otherwise release the subject's personal and private information.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation.

10.2 Clinical Investigation Finances and Agreements

The clinical investigation will be financed by Abbott. Investigational sites will be compensated by Abbott for participation in the clinical investigation per the conditions of agreement between the Sponsor and the Investigational site.

10.3 CIP Amendments

Approved CIP amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Principal Investigator is responsible for notifying the IRB/EC or equivalent committee of the CIP amendment (administrative changes) or obtaining IRB's/EC's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

Acknowledgement/approval by the IRB of the CIP amendment must be documented in writing prior to implementation of the CIP amendment. Copies of this documentation must also be provided to the Sponsor.

10.4 Training

10.4.1 Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and clinical investigation personnel will include, but is not limited to, the CIP requirements, device usage, electronic case report form completion and clinical investigation personnel responsibilities. All

Investigators and clinical investigation personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and clinical investigation personnel must not perform any CIP-related activities that are not considered standard of care at the site.

10.5 Monitoring

Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations, and has signed the Investigator Agreement
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Source documentation (including original medical records) must be available to substantiate proper informed consent procedures, adherence to CIP procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.
- The Investigator/site will permit access to such records. A monitoring visit sign-in log will be maintained at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical investigation-related documents.

10.6 Deviations from CIP

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing.

No waivers for CIP deviations will be granted by the Sponsor. All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of CIP deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB/EC or equivalent committee of all CIP deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, Sponsor may terminate the investigator's participation in the clinical investigation.

10.7 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection during a Quality Assurance audit.

In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

10.8 Sponsor Auditing

1. The Sponsor shall prepare an audit plan as well as the operating procedures for the related duties and conduct audits in accordance with the audit plan and the operating procedures.

2. Individual engaged in auditing (hereinafter referred to as "auditor") shall be different than those in charge of medical device development or monitoring.

3. The auditor shall prepare an audit report documenting the matters confirmed in the audit to certify and verify that the audit has been conducted and submit them to the Sponsor.

10.9 Committees

10.9.1 Steering Committee

The Steering Committee is responsible for overseeing the scientific and operational aspects of the clinical investigation. This committee will meet regularly to monitor subject enrollment, general data collection and non-compliance with the CIP at individual centers, to review operational issues that may arise and warrant a CIP amendment or other corrective action and to determine policy regarding any publications arising from data generated from the performance of the clinical investigation.

10.9.2 Publications Committee

A Publication Committee may be established to oversee clinical investigations publications, including publication planning and authorship determinations. Publication Committee membership may include, Principal Investigator, a representative of the Sponsor and a statistician. The Publication Committee will determine policy and strategies regarding individual presentations and/or publications arising from clinical investigation generated data. The committee will also review all external requests for accessing clinical investigation-related data and strategies aligning with the Sponsor's presentation and publication team expectations. The committee will also follow the Sponsor's applicable policies and Standard Operating Procedures.

11.0 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the Electronic Data Capture (EDC) system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

At the conclusion of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites.

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, correspondence with the IRB/EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a 'need to know' basis, including periodic review of access rights, and revocation of access when an individual's employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to transfer into Sponsor's data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such

as the patient's medical condition, treatment, dates of treatment, etc. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document controlled.

11.3 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- CIP-required laboratory reports and 12-lead ECGs, reviewed and annotated for clinical significance of out of range results (if applicable).

  Note: With electronic medical records some clinical sites may be able to annotate that the labs or ECG have been reviewed in the system. For those sites that do not have such capability, the labs or ECG may be able to be printed or signed.

- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF
- Patient reported outcome measures may be completed using CRF worksheets. These serve as the source documentation.

11.4 Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and CRF completion. The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Data on CRFs will be collected for all subjects who sign an informed consent form, including subjects who may not meet all inclusion/exclusion criteria during screening at the index procedure.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. An electronic audit trail will be used to track any subsequent changes of the entered data.

11.5 Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

11.6 Devices Accountability

The VFR study is an investigation using market released medical devices and device accountability is not required.

12.0 ETHICAL CONSIDERATION

12.1 Institutional Review Board Review and Approval

Institutional Review Board (IRB) approval for the CIP and ICF/other written information provided to the patient will be obtained by the Principal Investigator at each investigational site prior to consenting and enrolling patients in this clinical investigation. The approval letter must be received prior to the start of this clinical investigation and a copy must be provided to the Sponsor.

Any amendments to the CIP as well as associated ICF changes will be submitted to the IRB and written approval obtained prior to implementation, according to each institution's IRB requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical investigation is completed, the Investigator will advise his/her IRB of the progress of this clinical investigation, per IRB requirements. Written approval must be obtained from the IRB yearly to continue the clinical investigation, or according to each institution's IRB requirements.

No investigative procedures other than those defined in this CIP will be undertaken on the enrolled subjects without the written agreement of the IRB and the Sponsor.

13.0 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure.

14.0 PUBLICATION POLICY

The data and results from the clinical investigation are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation. The Investigators will not use this clinical investigation-related data without the written consent of the Sponsor for any purpose other than for clinical investigation completion or for generation of publication materials, as referenced in the Clinical Trial Agreement. Single-center results are not allowed to be published or presented before the multi-center results. Any proposals for publications or presentations by the investigators must be reviewed and approved by the Sponsor in a timely manner to enable Sponsor review in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

The Sponsor will be responsible for determining whether to register the clinical investigation on www.clinicaltrials.gov or any other clinical trials, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. In the event Sponsor determines that the clinical investigation should be registered, Sponsor shall be responsible for any such registration and results posting as required by the ClinicalTrials.gov website. Institution and/or Principal Investigator(s) shall not take any action to register the clinical investigation.

15.0 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

The Virtual Flow Reserve (VFR) software provides an estimate of FFR to facilitate the assessment of the hemodynamic significance of coronary lesions imaged by optical coherence tomography (OCT). VFR and FFR have the same mathematical definition, but VFR is based on model-derived pressure losses rather than measured pressure losses. FFR has been a useful tool to assess the functional severity of a

stenotic lesion in a coronary artery and determine the need for revascularization in many clinical studies (1,2); VFR is expected to provide this same benefit that FFR provides to the clinician.

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with PressureWire and OCT imaging system, together with their likely incidence, are described in the IFU and **Appendix IV**. There may be risks related to the device to be used in this investigation that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

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15.3 Residual Risks Associated with the Device Under Investigation, as Identified in the Risk Analysis Report

The residual risks to the patient were identified from literature review or the complaint data review.

15.4 Risks Associated with Participation in this Clinical Investigation

The risks related to the procedure have been included in **Appendix IV**.

15.5 Steps Taken to Control or Mitigate Risks

In-depth recommendations, special precautions and instructions regarding patient selection, device handling, device placement and system removal are included in the IFU.

Risks associated with the use of PressureWire and OCT Imaging system during this clinical study are minimized through investigator selection and training, pre-specified patient eligibility requirements, and study monitoring to ensure adherence to the protocol.

These risk management aspects are detailed below:

Investigator Selection and Training: It is also stated in the IFU that the devices can only be used by physicians who have received appropriate training on how to use the device. This statement is interpreted to mean that the physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the devices including the surgical and/or non-surgical treatment of these conditions.

• Only physicians who are skilled in the manipulation of catheter-based technology in the vasculature and heart and have a good understanding of the risks associated with these manipulations, will be selected as investigators for this trial.

• Emergency surgical back-up should be available as per the institution's standard procedures.

•Preparation of the PressureWire and Dragonfly Imaging Catheter device and performance of the ILUMIEN OPTIS, OPTIS Integrated, and OPTIS Mobile systems will be in accordance with the device IFUs

• Training of Investigators on the CIP

• Pre-specified patient eligibility requirements - as stated in **Section 5** of the protocol.

Ensuring strict adherence to the clinical investigation protocol

The clinical investigation will be carefully monitored by the Sponsor monitor (or designee) to ensure adherence to the Clinical Investigational Plan. Adverse events and device deficiencies will be reported to Abbott/designee and will be monitored internally for safety surveillance purposes.

15.6 Risk to Benefit Rationale

The foreseeable rates of the anticipated adverse events associated with the procedure of FFR and OCT imaging systems are all below 10% (see **Appendix IV**). Moreover, as detailed in **Section 15.1**, evidence indicates that use of physiological measurements, such as VFR and FFR, in diagnosing the functional significance of coronary stenoses based on the lumen information obtained through OCT image pullback can potentially support the functional evaluation of coronary artery disease and procedural scenario planning can aid the decision-making of qualified clinicians, in conjunction with the clinical history and symptoms of patients as well as other diagnostic tests according to clinician's professional judgment. In turn, the following clinical benefits may be observed: (a) improved outcomes of PTCA (percutaneous transcutaneous coronary angioplasty), (b) reduced incidence of major adverse coronary events in patients being treated for complex CAD (coronary artery disease), (c) improved accuracy in the identification of hemodynamically relevant stenosis compared to use of angiography alone, and (d) reduced mortality and myocardial infarction compared to use of angiography alone.

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APPENDIX I: ABBREVIATIONS AND ACRONYMS

Acronym or Abbreviation	Complete Phrase or Definition
AE	Adverse Event
ADE	Adverse Device Effect
AUC	Area under curve
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
FDA	Food and Drug Administration
FN	False Negative
FP	False Positive
CRF	Case Report Form
DD	Device Deficiency
dL	Deciliter
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration (U.S.)
FFR	Fractional Flow Reserve
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institution Review Board
LAR	Legally Acceptable Representative
LCB	Lower Confidence Bound
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
mm	Millimeter

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Acronym or Abbreviation	Complete Phrase or Definition
NPV	Negative Predictive Value
NSTEMI	Non-ST Elevation Myocardial Infarction
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
Pa	Aortic Pressure
PCI	Percutaneous Coronary Intervention
Pd	Distal Coronary Arterial Pressure
PG	Performance Goal
PPV	Positive Predictive Value
RFR	Resting Full-cycle Ratio
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
STEMI	ST Elevation Myocardial Infarction
TIMI	Thrombolysis in Myocardial Infarction
TN	True Negative
TP	True Positive
US	United States
VFR	Virtual Flow Reserve

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APPENDIX II: DEFINITIONS

Adverse Event (AE):

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device under clinical investigation.

This definition includes events related to the investigational medical device or the comparator.

This definition includes events related to the procedures involved.

Serious Adverse Event (SAE):

An adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:
  - a life-threatening illness or injury OR
  - a permanent impairment to a body structure or a body function OR
  - an in-patient or prolonged hospitalization OR
  - a medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function OR
  - chronic disease
- Fetal distress, fetal death or a congenital abnormality or birth defect

A planned hospitalization for a pre-existing condition, or a procedure required by the CIP is not considered a serious adverse event.

Adverse Device Effect (ADE):

An adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from the use error or from intentional misuse of the investigational medical device.

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Serious Adverse Device Effect (SADE):

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Device Deficiency (DD):

A Device Deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling.

Thrombolysis in Myocardial Infarction (TIMI) Flow Grading System:

Grade 0 (no perfusion): There is no antegrade flow beyond the point of occlusion.

Grade 1 (penetration without perfusion): The contrast material passes beyond the area of obstruction but “hangs up” and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine-angiographic filming sequence.

Grade 2 (partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) is perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel (e.g., the opposite coronary artery or the coronary bed proximal to the obstruction).

Grade 3 (complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed from the involved bed and is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

NYHA Classification:

Class I: Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina pain.

Class II: Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III: Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV: Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

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Reference Vessel Diameter (RVD):

Average diameter of proximal and distal healthy segments by visual estimation. “Normal” reference segments are selected proximal and distal to the stenosis and averaged to define the reference vessel diameter.

Minimum Lumen Diameter (MLD):

The smallest measured luminal diameter in a diseased segment (as measured by visual estimation).

Percent Diameter Stenosis:

The value calculated as 100 * (1 - MLD/RVD) using the mean values from two orthogonal views (when possible) by visual estimation

Severe Valvular Disease:
According to 2017 American Heart Association/American College of Cardiology (AHA/ACC) Guidelines describe severe stages in the progression of valvular heart disease (VHD)

Stage	Definition	Description
C	Asymptomatic severe	Asymptomatic patients who have reached the criteria for severe VHD C1: Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated C2: Asymptomatic patients who have severe VHD, with decompensation of the left or right ventricle
D	Symptomatic severe	Patients who have developed symptoms as a result of VHD

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APPENDIX III: SITE CONTACT INFORMATION

A list of trial site coordinators can be obtained upon request from the Clinical Project Manager for the clinical investigation.

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APPENDIX IV: RATES OF FORESEEABLE ADVERSE EVENTS

The anticipated potential adverse events with corresponding rates are shown in Tables A and B below.

TABLE A: ANTICIPATED ADVERSE EVENTS AND RATES FOR FFR

Anticipated Adverse Events for FFR	**Frequency Rate Ranges**			
Category	**POSSIBLE (≥ 0.5%)**	**UNLIKELY (≥ 0.1 but < 0.5%)**	**REMOTE (≥ 0.001% but < 0.1%)**	**EXTREMELY UNLIKELY (< 0.001%)**
Bleeding	**X**			
Hypotension		**X**		
Chest pain	**X**			
Vessel dissection or occlusion		**X**		
Perforation (vascular perforation)		**X**		
Spasm or abrupt closure				**X**
Serious arrhythmias	**X**			
Myocardial infarction	**X**			
Congestive heart failure		**X**		
Embolus		**X**		
Thrombosis		30 days follow up - **X** ≥ 1 year follow-up - **X**		
Cardiac tamponade/pericardial effusion		**X**		
Prolonged procedure		**X**		
Foreign body in patient				**X**
Urgent revascularization	**X**			
Pneumothorax				**X**
Stroke/cerebral vascular accident (CVA)/transient ischemic attack (TIA)	**X**			
Local and/or systemic infection		**X**		
Renal insufficiency				**X**
Death	**X**			
Device-related events		**X**		

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TABLE B: ANTICIPATED ADVERSE EVENTS AND RATES FOR OCT

Anticipated Adverse Events for OCT	Frequency Rate Ranges			
Category	**POSSIBLE (≥ 0.5%)**	**UNLIKELY (≥ 0.1 but < 0.5%)**	**REMOTE (≥ 0.001% but < 0.1%)**	**EXTREMELY UNLIKELY (< 0.001%)**
Allergic reaction to the contrast media or drug administered for the procedure		X		
Bleeding	X			
Arterial dissection, injury or perforation	X			
Abnormal heart rhythm or arrhythmias	X			
Unstable angina	X			
Coronary artery spasm	X			
Thrombus formation, abrupt closure, or total occlusion	X			
Embolism				X
Myocardial ischemia	X			
Acute myocardial infarction	X			
Repeat revascularization	X			
Renal insufficiency or failure from contrast media use	X			
Death	X			
Catheter access site reactions: sterile inflammation or granuloma				X
Tissue necrosis				X

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APPENDIX V: CASE REPORT FORMS

The Final Case Report Forms will be provided under a separate cover as part of pertinent regulatory submissions and study documentation/information to clinical sites.

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APPENDIX VI: INFORMED CONSENT FORM

The Final Informed Consent Form will be provided under a separate cover as part of pertinent regulatory submissions and study documentation/information to clinical sites.

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APPENDIX VII: MONITORING PLAN

A copy of the Monitoring Plan can be obtained upon request from the Sponsor Clinical Project Manager for the clinical investigation.

Clinical Investigation Plan

APPENDIX VIII: REVISION HISTORY

Administrative changes such as changes in version, document date, reference numbering and sponsor personnel as well as editorial and grammatical changes are not captured in this table.

Amendment Number	Version	Date	Key Revision Summary
Not Applicable	A	23JAN2020	First release of CIP

1	B	15JUN2020	• Addition of Steering Committee in the study
			• Addition of subgroup analysis
			  ○ Diabetes vs Non-diabetes
			  ○ Pre-PCI vs Post-PCI
			• Additional clarification on enrollment in ICF section
			  ○ Subjects who signed an Informed Consent form and met general inclusion criteria and no exclusion criteria and will participate in the clinical investigation
			• Additional clarification on AE collection ending timepoint
			  ○ Study participation ends when the subject leaves the catheterization laboratory.
			• Removal of UADE throughout the CIP
			• Explanation on multivessel and staged procedure
			• Clarification on limit number of vessels per patient.
			  ○ There is no limit on the number of vessels per patient if the vessels met all inclusion and exclusion criteria.
			• Changing amount of nitroglycerin from 200 µg to at least 100 µg
			• Addition of post-PCI angiography step
			• Changing number of participated sites from 20 to 25 sites
			• Changing exclusion criteria on known renal insufficiency from eGFR < 45 ml/kg/m^2 to be eGFR < 30 ml/kg/m^2
			• Addition of LVEF and NYHA assessments in schedule of events

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			• Additional language on collecting and uploading intermediate OCT pullbacks
			• Revision on pressure drift guideline to be consistent throughout the CIP
			  ○ Pressure drift of > 3 mmHg
			• Addition of 3 additional imaging exclusion criteria
			  ○ Severe vessel tortuosity or calcification in the target vessel such that it is unlikely that the OCT catheter can be delivered
			  ○ Inability to receive intracoronary nitroglycerin prior to OCT or FFR
			  ○ Use of flush media other than radiographic contrast
			• Addition of a general exclusion on COVID-19
			  ○ Subject had active COVID-19 symptoms and/or a positive test result within the prior 2 months

2	C	16JUL2020	• Addition of hematocrit to baseline assessment
			• Addition of a general exclusion criteria on double enrollment in clinical study
			  ○ Participation in another clinical study of an investigational drug or device
			• Add definition on qualified OCT pullback image length
			  ○ OCT pullback image will be qualified as long as all disease segment was captured
			• Revision on pressure drift guideline according to core laboratory definition
			  ○ Pressure drift of > 0.03; i.e. Pd and Pa ratio value < 0.97 or > 1.03, unless physiology measurements are repeated after re-equalization

3	D	3SEP2020	• Clarification and addition of silent ischemia in general exclusion criteria ○ Clinical presentation with or history of stable angina, unstable angina, or silent ischemia (defined as abnormal stress test or abnormal invasive physiology assessment) that has led to the procedure • Removal of site study investigator and study principle investigator signature pages as the study is conducted in US only

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			• Changing number of participated sites from 25 to 30 sites

4	E	28JAN21	• Change the number of a sample size from 233 to 310 and update sample size language with no dual vessel and positive FFR post-PCI assumption
			• Remove patient cap per site
			• Change duration of enrollment to 15 months and the total study duration to be 27 months
			• Add a clarification on the bifurcation lesions and flowchart
			• Add additional information on general exclusion criteria
			  ○ Severe valvular heart disease or history of valve repair or replacement
			  ○ Presence of any myocardial bridge (MB), regardless of vessel location
			• Add a clarification on severe valvular disease
			• Change mandatory post-PCI data collection step to optional
			• Add additional details on pressure drift checking
			• Add additional details on checking OCT pullback after the run to ensure all lesion segments are captured
			• Add clarification details on the blinding/unblinding step. Change flowchart diagram and frequency of OCT pullback transfer after a quality check from core laboratory to be every 50 patients instead of at the end of the enrollment to facilitate faster analysis of the VFR
			• Correct the order of guidewire removal timepoint in procedure step in **Appendix XI**

5	F	14APR21	• Change the pre-PCI procedure order to have physiological measurement conducted first before OCT imaging • Change 5.5 section heading from ‘subject withdrawal’ to ‘subject discontinuation’ • Add statement on protocol deviation in Section 3.2.2, ‘If the enrollment cap is implemented, protocol deviation(s) will be given if the sites do not follow the capping criteria.’ • Add a new general exclusion criteria

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- Presence of aneurysm in the target vessel

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APPENDIX IX: CIP SUMMARY

Clinical Investigation Name and Number	CRD_1006 FUSION
Title	Validation of OCT-based **FU**nctional diagno**SI**s of cor**ON**ary stenosis (FUSION)
Objective(s)	To validate the diagnostic performance of VFR by comparing it against a reference standard, fractional flow reserve (FFR)
Number of Subjects Required for Inclusion in Clinical Investigation	N = 310 Up to 30 centers in the US
Clinical Investigation Design	Prospective, single-arm, multi-center
Primary Endpoint(s)	Sensitivity and specificity of VFR against FFR
Secondary Endpoints	• Overall diagnostic accuracy • Positive predictive value (PPV) • Negative predictive value (NPV) • Correlation between VFR and FFR • Area under curve (AUC) against FFR
Subject Follow-up	No follow-up
Inclusion Criteria	• Age ≥18 years • Patient provides written informed consent • Scheduled for clinically indicated coronary catheterization with the intent to perform physiologic assessment to guide physician clinical course (in lesions with visual % diameter stenosis 40-90%), if clinically indicated • Subject is undergoing invasive FFR with Adenosine (high-dose intra-coronary (IC) [200 µg for the left and or 100 µg for the right coronary artery] or 140 µg/kg/min for intravenous (IV)) used as hyperemic stimulus • Clinical presentation with or history of stable angina, unstable angina, or silent ischemia (defined as abnormal stress test or abnormal invasive physiology assessment) that has led to the procedure
General Exclusion Criteria	• Prior history of myocardial infarction (MI) in the target vessel • Presence of acute ST Elevation Myocardial Infarction (STEMI)

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	• Culprit vessel of Non-ST Elevation Myocardial Infarction (NSTEMI) • TIMI flow < Grade 3 at baseline or visible thrombus • Prior history of coronary artery bypass grafting (CABG) • Prior heart transplant • Severe valvular heart disease or history of valve repair or replacement • Prior history of PCI with stent in target vessel, or target vessel involves in-stent restenosis. • Target coronary vessel is supplied by major collaterals or is supplying major collaterals to a CTO (chronic total occlusion) • CTO in the target vessel • Severe diffuse disease observed in target vessel defined as the presence of diffuse, serial gross luminal irregularities present in the majority of the coronary tree • Presence of any myocardial bridge (MB), regardless of vessel location • Contraindication for FFR examination or administration of vasodilators • Known LVEF ≤45% • Target lesion involves Left Main coronary artery or ostial right coronary artery • Known renal insufficiency (eGFR < 30 ml/kg/m^2 or serum creatinine ≥ 2.5 mg/dL) • Heart Failure NYHA Class III or IV • Subject is pregnant (For a female subject of childbearing potential, a pregnancy test must be performed within 14 days (≤14 days) prior to the index procedure per site standard test) • Subject has or had active COVID-19 symptoms and/or a positive test result within the prior 2 months • Participation in another clinical study of an investigational drug or device • Presence of aneurysm in the target vessel
Imaging and Pressure Tracing Exclusion Criteria	• Artifact in pre-PCI OCT for the target lesion or in the event of multiple target lesions, artifact in pre-PCI OCT for ALL target lesions • Target lesion requires any preparation (including but not limited to balloon dilatation, atherectomy, etc.) prior to pre-PCI OCT and physiology measurements, or in case of multiple target lesions, ALL target lesions require any preparation (including but not limited to balloon dilatation, atherectomy, etc.) prior to pre-PCI OCT and physiology measurement

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	• Severe vessel tortuosity or calcification in the target vessel such that it is unlikely that the OCT catheter can be delivered • Target lesion not imaged by OCT or in the event of multiple target lesions, ALL target lesions not imaged by OCT • Pressure drift of > 0.03; i.e. Pd and Pa ratio value < 0.97 or > 1.03, unless physiology measurements are repeated after re-equalization • Target lesion or significant CAD beyond 60 mm from coronary ostium; i.e. not able to clearly image and capture all disease segment with OCT in 1 run. • Incorrectly done or unsuccessful catheter purge and/or contrast flush • Presence of plaque rupture and/or intravascular hematoma in target vessel (visual % diameter stenosis ≥ 40%) • Inability to receive intracoronary nitroglycerin prior to OCT or FFR • Use of flush media other than radiographic contrast

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APPENDIX X: REFERENCES

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APPENDIX XI: PROCEDURAL STEPS

The following sections outline procedural steps including co-registration of imaging and pressure measurements. In all cases, the investigator must adhere to the IFUs.

Any vessel preparation (if necessary) with balloon dilation or atherectomy must be performed only after pre-PCI physiological indices measurement and OCT have been performed.

Pre-PCI Angiography

1. Administer at least 100 µg of IC nitroglycerin.
2. Perform 2-contralateral cine angiograms of the culprit vessel without panning.

Pre-PCI Physiological Indices

1. Zero aortic transducer.
2. Flush and zero PressureWire™ outside the body.
3. Administer at least 100 µg of IC nitroglycerin.
4. Advance PressureWire to equalize position (guide disengaged).
5. Flush the guiding catheter to ensure appropriate aortic waveform (dicrotic notch).
6. Equalize PressureWire.
7. Remove any other coronary wires from within the target vessel.
8. Advance the PressureWire at least 10 mm distal to the most distal target lesion.
9. Document PressureWire position with cine documentation with contrast administration.
10. Flush the guiding catheter with saline.
11. Record the baseline blood pressure (with confirmation of distinct dicrotic notch with guide disengaged).
12. Capture Pd/Pa and RFR snapshots.
13. Induce maximal hyperemia with Adenosine per standard institutional practice (140 µg/kg/min IV or high dose 200 µg or 100 µg for the left or right coronary artery IC adenosine, respectively).
14. Record FFR.
15. Wait until hyperemia has worn off by confirming Pd/Pa has returned to the resting value.
    a. 1 minute following IC administration
    b. 3 minutes following IV administration
16. Record for RFR pullback (0.5mm/sec).
17. Check for pressure drift (i.e. range on 0.97-1.03 is accepted) and record the Pd/Pa snapshot value in FFR mode. If drift is present, physiology measurements are repeated after re-equalization at the aorto-ostial junction.
18. Remove PressureWire.
19. Upon completion of physiological measurement, record device lot and model numbers
20. Complete Adverse Event eCRF, if applicable (adverse device effects).

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Pre-PCI OCT

1. Administer at least 100 µg of IC nitroglycerin if more than 10 minutes has passed since last dose.
2. Introduce and position the Dragonfly™ lens into the distal coronary artery at the same location as the PressureWire sensor, beyond all suspect lesions with the aim of capturing as much of the coronary artery as possible.
3. Record proximal and distal frames.
4. Capture lens position via cine documentation prior to each pullback.
5. Set the motorized pullback device on the “Survey Mode” at 75 mm pullback.
6. Perform OCT pullback per IFU instruction and simultaneously perform cine angiography without panning in the desired angiographic co-registration view(s) during OCT pullback.
7. Check the quality of the pullback. If the pullback started in the middle of the lesion, this pullback needs to be redone more distally to capture all the lesions segment. If there is presence of plaque rupture, hematoma, or thrombus within the pullback, this patient is a screen fail.
8. Record contrast injection method and amount.
9. Remove the OCT catheter.
10. Upon completion of OCT, record device lot and model numbers.
11. Complete Adverse Event eCRF, if applicable (adverse device effects).

If the subject is no longer deemed a candidate for PCI, or the investigator decides not to continue with the PCI, this is the end of protocol for the subject.

PCI (if applicable)

1. Perform PCI as per standard practice.
2. Record the PCI procedure details on the eCRF.
3. Complete Adverse Event eCRF, if applicable (adverse events).

Post-PCI study data collection step is optional but strongly recommended. If the post-PCI study data collection step is decided to be carried out, both the post-PCI OCT pullback and physiological assessment should be performed. If the subject had undergone atherectomy during PCI, post-PCI OCT and physiological steps are not required and that is the end of the protocol for the subject.

(Optional) Final Post-PCI OCT

This should be the final OCT following PCI/optimization, the time at which the wires would otherwise be removed for ending the procedure.

1. Administer at least 100 µg of IC nitroglycerin.
2. Introduce and position the Dragonfly lens into the distal coronary artery, beyond treated segment and all suspect lesions, at least 10 mm distal to the stent or more distal lesion with the aim of capturing as much of the coronary artery as possible.
3. Capture lens position via cine documentation prior to each pullback.
4. Ensure the motorized pullback device is set to “Survey Mode” 75 mm pullback.
5. Perform OCT pullback per IFU instruction and simultaneously perform cine angiography without panning in the desired angiographic co-registration view(s) during OCT pullback

6. Record contrast injection method and amount.
7. Remove the OCT catheter.
8. Upon completion of OCT, record device lot and model numbers.
9. Complete Adverse Event eCRF, if applicable (adverse device effects).

(Optional) Post-PCI Physiological Indices

1. Perform post-PCI physiological measurements according to the procedural steps outline in '**Pre-PCI Physiological Indices'.**

(Optional) Post-PCI Angiography

1. Administer at least 100 µg of IC nitroglycerin.
2. Perform 2-contralateral cine angiograms of the culprit vessel without panning.

All pressure tracings, angiographic and OCT data will be stored digitally for subsequent analysis and these deidentified images and tracings must be uploaded to BioClinica and sent to the Core Laboratory for quality check.