Abbott	Clinical Investigation Plan Cover Page

NCT Number: 03507777
ILUMIEN IV: OPTIMAL PCI
OPtical Coherence Tomography (OCT) Guided Coronary Stent IMplantation Compared to Angiography: a Multicenter Randomized TriaL in PCI
[redacted]
[redacted]
Date: 6-OCT-2022

Sponsor Abbott

[redacted]

ILUMIEN IV: OPTIMAL PCI

CLINICAL INVESTIGATION PLAN

OPtical Coherence Tomography (OCT) Guided Coronary Stent IMplantation Compared to Angiography: a Multicenter Randomized TriaL in PCI

[redacted]

ILUMIEN IV: OPTIMAL PCI
OPtical Coherence Tomography (OCT) Guided Coronary Stent IMplantation Compared to Angiography: a Multicenter Randomized TriaL in PCI
[redacted]
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[redacted]
Clinical Investigation Plan (CIP)

Sponsor	Abbott [redacted]
Co-Principal Investigator	[redacted]
Co-Principal Investigator	[redacted]
Chairman	[redacted]
Angiographic and Optical Coherence Tomography Core Laboratory	[redacted]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Principal Investigator

Printed name:
Signature:
Date:

Principal Investigator

Printed name:
Signature:
Date:

Chairman

SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Chairman

Printed name: [redacted]
Signature:
Date:

STUDY SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Principal Investigator

Printed name:
Signature:
Date:

Principal Investigator

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Date:

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1 Synopsis

1.1 Objective

The objective of this clinical investigation is to demonstrate the superiority of an Optical Coherence Tomography (OCT)-guided stent implantation strategy as compared to an angiography-guided stent implantation strategy in achieving larger post-PCI lumen dimensions and improving clinical cardiovascular outcomes in patients with high-risk clinical characteristics and/or with high-risk angiographic lesions. In addition, embedded within the ILUMIEN IV protocol is a separate pre-specified powered analysis of XIENCE to be conducted in randomized ILUMIEN IV subjects with in-stent restenosis (ISR). The objective of the analysis is to demonstrate the safety and effectiveness of XIENCE in the treatment of ISR lesions. This is described in further detail in **Appendix F**.

1.2 Hypothesis

See **Section 7.1.1 (Primary Endpoint of Minimum Stent Area (MSA) and Hypothesis)** and **Section 7.1.2 (Co-Primary Endpoint of TVF and Hypothesis)** for details.

1.3 Devices Used

[redacted]

[redacted]

[redacted]

1.4 Indications for Use

[redacted]

[redacted]

1.5 Design

This is a prospective, single-blind clinical investigation randomizing subjects to OCT-guided coronary stent implantation vs. angiography-guided coronary stent implantation in a 1:1 ratio. The clinical investigation will be conducted at approximately 125 centers in North America (US and Canada), Europe, Middle East and Asia-Pacific. Up to 3656 randomized subjects and approximately 375 roll-in subjects will be enrolled in the clinical investigation. No site may enroll more than 15% of the total randomized subjects. Subjects participating in this clinical investigation will be followed for 2 years. [redacted]

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risks and Benefits section of this clinical investigation plan for details.

1.6 Endpoints

There are two powered primary endpoints, one powered major secondary endpoint and multiple descriptive non-powered secondary endpoints in this clinical investigation. Definitions of endpoints can be found in **Appendix B**.

1.6.1 Primary Endpoints

1. Imaging Outcome (powered): Minimal stent area (MSA), continuous measure

   Final Post-PCI MSA (per target lesion basis) assessed by OCT in each randomized arm, measured at an independent OCT core laboratory blinded to imaging modality assignment.

2. Clinical outcome (powered): Target vessel failure (TVF)

   Time-to-first event rate of the composite outcome of cardiac death, target vessel myocardial infarction (TV-MI) (per primary protocol definition [see Appendix B]), or ischemia-driven target vessel revascularization (ID-TVR), assessed at 2 years.

1.6.2 Major Secondary Endpoint

1) Target vessel failure (TVF) excluding periprocedural MI.

   Time-to-first event rate of the composite outcome of cardiac death, target vessel-related spontaneous myocardial infarction, or ischemia-driven target vessel revascularization (ID-TVR), assessed at 2 years.

1.6.3 Non-Powered Secondary Endpoints

Procedural outcomes, additional procedural and clinical endpoints, patient reported outcomes (PRO) and cost-effectiveness measures listed below

Procedural outcomes

OCT-defined (OCT core laboratory assessed). Subjects in the angiography-guided arm will undergo a post-PCI OCT run, blinded to the operator. Assessed per target lesion.

1) Stent expansion. Stent expansion is defined by the MSA achieved in the proximal and distal stented segments relative to their respective reference lumen areas. The stent length is divided into 2 equal segments (proximal and distal) except for lesions containing a bifurcation (visually estimated side branch ≥2.5 mm). When there is a bifurcation present, rather than splitting the stent into two halves, the division occurs at the proximal most side branch.

   - Acceptable stent expansion (categorical variable): The MSA of the proximal segment is ≥90% of the proximal reference lumen area and the MSA of the distal segment is ≥90% of the distal reference lumen area.

   - Unacceptable stent expansion (categorical variable): The MSA of the proximal segment is <90% of the proximal reference lumen area, and/or the MSA of the distal segment is <90% of the distal reference lumen area.

   In case either segment (proximal or distal) of the stent meets criteria for unacceptable stent expansion, the stent is considered to have unacceptable stent expansion. Both segments of the stent must meet acceptable stent expansion criteria to be considered acceptable.

   In case a respective reference segment cannot be measured the determination will be made with only one of the two reference (proximal or distal) segments.

   Note: If acceptable stent expansion (by operator assessment) is not achieved in either the distal or proximal segments of the stent in the OCT-guided arm according to the Post-PCI OCT, further post-stent expansion with higher pressures and/or larger balloons must be performed per protocol if the POST-PCI OCT EEL measurements now suggest a larger balloon be used. See ***Section 6.5.3.7*** *for more details.*

   - Post-PCI stent expansion (%) (continuous variable): The MSA divided by the average of proximal and distal reference lumen areas x 100.

2) Mean stent expansion (%) (continuous variable): The mean stent area (stent volume/analysed stent length) divided by the average of proximal and distal reference lumen areas x 100.

3) Intra-stent plaque protrusion and thrombus

Defined as a mass attached to the luminal surface or floating within the lumen, meeting the following criteria: Protrusion/thrombus is defined as any intraluminal mass protruding at least 0.2 mm within the luminal edge of a stent strut, and will be further classified as Major and Minor:

- Major: Protrusion area/Stent area at site of tissue protrusion ≥10% and the minimal intrastent flow area (MSA – protrusion area) is unacceptable (<90% of respective proximal or distal reference area
- Minor: Protrusion area/Stent area at site of tissue protrusion is <10%, or is ≥10% but the minimal intraluminal flow area (MSA – protrusion area) is acceptable (≥90% of respective proximal or distal reference area

Note: It is recommended that if protrusion is detected by operator assessment in the OCT-guided arm during the procedure and meets the criteria for major protrusion, then thrombus aspiration, further high-pressure balloon inflation and/or an additional stent be considered.

4) Untreated reference segment disease

Defined as focal disease with untreated MLA <4.5 mm^2 within 5 mm from the proximal and/or distal stent edges.

Sub-classified by the amount of untreated lipid plaque, divided into 3 grades:

i. Low (≤90° of lipid arc)

ii. Medium (>90°-<180° of lipid arc)

iii. High (≥180° of lipid arc)

Note: If untreated reference segment disease with an MLA <4.5 mm^2 is detected by operator assessment in either the proximal reference (inflow disease) or distal reference (outflow disease) segment lumen in the OCT-guided arm, an additional stent must be placed to treat it, unless there are anatomic reasons that the disease should not be covered (e.g. diffuse distal disease or significant vessel tapering, etc.) (Figures 1a-b).

5) Edge dissections

Edge dissections will be tabulated as:

i. Major (%): ≥60 degrees of the circumference of the vessel at site of dissection and ≥3 mm in length

ii. Minor (%): any visible edge dissection <60 degrees of the circumference of the vessel or <3 mm in length

Edge dissections will be further classified as:

i. Intimal (limited to the intima layer, i.e. not extending beyond the internal elastic lamina)

ii. Medial (extending into the media layer)

iii. Adventitial (extending through the external elastic membrane/lamina)

Note: If a major edge dissection is detected by operator assessment in the OCT-guided arm, it is recommended that an additional stent be placed to cover the dissected segment, particularly if the site of dissection is at the distal stent edge.

6) Stent Malapposition

Defined as frequency (%) of incompletely apposed stent struts (defined as stent struts clearly separated from the vessel wall (lumen border/plaque surface) without any tissue behind the struts with a distance from the adjacent intima of ≥0.2 mm and not associated with any side branch).

Malapposition will be further classified as:

- Major: if associated with unacceptable stent expansion (as defined above)
- Minor: if associated with acceptable stent expansion (as defined above)

Note: If malapposition is detected by operator assessment during the procedure in the OCT-guided arm and meets the criteria for major malapposition (i.e. malapposition associated with unacceptable stent expansion), further stent expansion must be performed. The degree of stent underexpansion (acceptable or unacceptable) should guide the intervention rather than amount of malapposition.

Stent Malapposition will be tabulated as:

i. Major (%)
ii. Minor (%)
iii. All (Major and Minor) (%)

7) Border detection (angiography arm post-PCI only, blinded to investigator)

The visibility of the vessel external elastic lamina (EEL) border by OCT will be evaluated at both reference sites (proximal and distal) and the MSA, after intervention and then classified into 3 grades:

i. Good: ≥75% (270°) of visible circumference
ii. Moderate: ≥50% (180°) - <75% (270°) of visible circumference
iii. Poor: <50% (180°) of visible circumference

8) Intra-stent lumen area (intra-stent flow area)

Defined as stent area minus any protrusion as defined above in secondary endpoint 3).

9) Effective lumen area (total flow area)

Defined as intra-stent lumen area plus any area of malapposition between the stent and the vessel wall (lumen border/plaque border).

Additional Procedural and Clinical Endpoints

10) Angiographic Endpoints (QCA). (Angiographic core laboratory assessed). Assessed per target lesion.

i. Final (post-PCI) minimal lumen diameter
ii. Final (post-PCI) percent diameter stenosis
iii. Acute lumen gain post-intervention
iv. Maximum device size (stent or post-dilatation balloon)/reference vessel diameter ratio
v. Post-PCI target vessel TIMI flow rate

vi. Angiographic complications – worst (anytime during the procedure) and final (post PCI and all imaging) – Angiographic dissection ≥ NHLBI type B, perforations (Ellis classification), intra-procedural thrombotic events (including slow-flow, no-reflow, side branch closure, distal embolization, and intra-procedural stent thrombosis, as per the standard angiographic core laboratory definitions

11) Device Usage Endpoints (site reported; assessed per subject):

i. Total stent length
ii. Total number of stents
iii. Maximal stent size
iv. Post dilatation (yes/no)
v. Total number of post-dilatation balloons
vi. Maximal post-dilatation balloon size
vii. Maximal device size (stent or post-dilatation balloon)
viii. Maximum inflation pressure (atm.; stent or post-dilatation balloon)

12) Procedure time (first wire insertion to guide catheter removal), fluoroscopy time, radiation exposure

13) Contrast use; contrast induced nephropathy (defined as serum creatinine rise >25% or absolute increase >0.5 mg/dL (44.2µmol/L)); need for renal replacement therapy

14) Procedural success (must be present in all treated lesions and vessels):

Defined as A) angiographic core laboratory-assessed final (post-PCI) lesion angiographic diameter stenosis <30% and target vessel TIMI III flow without any of the angiographic complications listed in 10(vi) above; plus B) the absence of site-assessed prolonged ST-segment elevation or depression (>30 minutes), cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation, or procedural death.

15) Procedural complications

Defined as A) angiographic core laboratory-assessed complications listed in 10(vi) above occurring anytime during the procedure; or B) site-assessed prolonged ST-segment elevation or depression (>30 minutes), cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation, or procedural death.

16) OCT performance success (site reported) (OCT arm only):

OCT imaging performed both pre- and post-PCI

17) OCT imaging-related procedural complications (CEC adjudicated)

Any procedural complications (e.g. angiographic dissection, perforation, thrombus, acute closure, etc.) requiring any active intervention (e.g. prolonged balloon inflations, additional stent implantation, pericardiocentesis, intubation, hemodynamic support or pressors, defibrillation or cardioversion) or death adjudicated by the CEC as definitely or likely attributable to the physical performance of OCT-imaging (e.g. passing the catheter through the vasculature or stent, or injecting contrast to clear the

blood for imaging). For this definition, adverse events that arise due to changes in PCI strategy as the result of OCT findings are NOT considered OCT imaging-related procedural complications.

18) Additional interventions on the basis of the pre-PCI or post-stent OCT-imaging run that would not have been performed based on angiographic guidance alone (site reported; assessed per subject; OCT Arm Only):

i. Use of larger balloon
ii. Use of higher inflation pressures
iii. Use of additional balloons
iv. Use of additional stent(s)
v. Performance of atherectomy
vi. Other interventions

Reason(s) for additional interventions will be documented by the site (e.g. more calcium than anticipated, greater stent under-expansion than appreciated angiographically, greater malapposition than appreciated angiographically, greater tissue protrusion or thrombus burden than appreciated angiographically, more severe edge dissection than appreciated angiographically, residual reference segment disease not appreciated angiographically, other)

Clinical outcomes at 30 days, 1 year and 2 years (unless otherwise noted)

19) Target lesion failure (TLF; cardiac death, TV-MI or ischemia-driven target lesion revascularization (ID-TLR)

20) All-cause mortality

21) Cardiac and non-cardiac mortality

22) All MI

23) TV-MI, non-TV-MI and indeterminate vessel MI

24) Periprocedural MI and non-periprocedural MI

25) All revascularization

26) ID-revascularization and non-ID-revascularization

27) ID-TVR, ID-TLR, ID-non-TLR TVR, and ID-non-TVR

28) Definite, probable and definite/probable stent thrombosis (ARC-2 definition)

29) Relationship between immediate post-procedure OCT parameters (e.g. MSA, procedural success, malapposition, dissection, protrusion, etc.) and 2-year endpoint rates (e.g. TVF, TLF, all-cause mortality, cardiac death, TV-MI, all MI, ID-TLR, ID-TVR, and stent thrombosis)

30) TVF excluding periprocedural MI (i.e. the composite of cardiac death, target vessel-related spontaneous MI, or ID-TVR) (at 30 days and 1 year)

In addition, the following outcomes using the SCAI definition of peri-procedural MI[3] will be reported as sensitivity analyses at 30 days, 1 year and 2 years:

31) TV-MI$_{SCAI}$ (periprocedural MI by SCAI definition and spontaneous MI by protocol definition)

32) Periprocedural MI$_{SCAI}$ (by SCAI definition)

33) All MI$_{SCAI}$ (periprocedural MI by SCAI definition and spontaneous MI by protocol definition)

34) TVF$_{SCAI}$; the composite of cardiac death, TV-MI$_{SCAI}$ or ID-TVR

Patient Reported Outcomes (PRO)

Patient Reported Outcome questionnaires will be incorporated into this study to provide a complementary evaluation of the effectiveness of OCT-guided stent implantation. The following instruments will be administered during this study in hospital (required at baseline, optional post-procedure), and at 30 day, 12 month and 24 month follow-up:

- EuroQoL 5D (EQ-5D-5L) survey to assess overall health status

Cost-effectiveness

Cost per quality adjusted life year (QALY) and TVF event prevented by OCT-guidance to be determined using standardized methods[4].

1.7 Study Population

The intended population for this clinical investigation is patients over the age of 18 years that are either high clinical-risk or have high angiographic-risk lesion characteristics undergoing stent implantation for coronary artery disease.

1.8 Inclusion/Exclusion Criteria

1.8.1 Inclusion Criteria (all must be present)

1. Subject must be at least 18 years of age.

2. Subject must have evidence of myocardial ischemia (e.g., stable angina, silent ischemia (ischemia in the absence of chest pain or other anginal equivalents), unstable angina, or acute myocardial infarction) suitable for elective PCI.

3. Patients undergoing planned XIENCE stent implantation during a clinically indicated PCI procedure meeting one or more of the following criteria:

[3] Moussa ID et al. Consideration of a New Definition of Clinically Relevant Myocardial Infarction After Coronary Revascularization: An Expert Consensus Document From the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol. 2013 October 22; 62(17): 1563–1570.
[4] Eisenberg J. Clinical economics: A guide to the economic analysis of clinical practices. JAMA 1989; 262:2879-86.

A) High clinical-risk, defined as;

i. Medication-treated diabetes mellitus, AND/OR

B) High angiographic-risk lesion(s), with at least one target lesion in each target vessel planned for randomization meeting at least one of the following criteria;

i. Target lesion is the culprit lesion responsible for either:
   - NSTEMI, defined as a clinical syndrome consistent with an acute coronary syndrome and a minimum troponin of 1 ng/dL (may or may not have returned to normal), OR
   - STEMI >24 hours from the onset of ischemic symptoms

ii. long or multiple lesions (defined as intended total stent length in any single target vessel ≥28 mm),

Note: For a long target lesion, this would permit treatment by a single long stent or overlapping stents.

Note: For up to two target lesions located in a single target vessel and treated with non-overlapping stents, they may be located in a continuous vessel or split up between a main vessel and a side branch.

iii. bifurcation intended to be treated with 2 planned stents (i.e. in both the main branch and side branch), and where the planned side branch stent is ≥ 2.5 mm in diameter by angiographic visual estimation.

iv. angiographic severe calcification (defined as angiographically visible calcification on both sides of the vessel wall in the absence of cardiac motion),

v. chronic total occlusion (CTO) (enrolment and randomization in this case performed only after successful antegrade wire escalation crossing and pre-dilatation)

vi. in-stent restenosis of diffuse or multi-focal pattern. Lesion must be at or within the existing stent margin(s) and have angiographically visually-assessed DS ≥70% or DS ≥50% with non-invasive or invasive evidence of ischemia

4. All target lesions (those lesions to be randomized) must have a visually estimated or quantitatively assessed %DS of either ≥70%, or ≥50% plus one or more of the following: an abnormal functional test (e.g. fractional flow reserve, stress test) signifying ischemia in the distribution of the target lesion(s) or biomarker positive ACS with plaque disruption or thrombus.

Note: For purposes of study eligibility, a minimum troponin of 1 ng/dL at the time of screening will be considered biomarker positive.

5. All target lesions must be planned for treatment with only ≥2.5 mm and ≤3.5 mm stents and post-dilatation balloons based on pre-PCI angiographic visual estimation.

6. No more than 2 target lesions requiring PCI are present in any single vessel., and no more than 2 target vessels are allowed. Thus, up to 4 randomized target lesions per patient in a maximum of 2 target vessels are allowed, including branches. The intended target lesions will be declared just prior to randomization.

Note: A lesion is defined as any segment(s) of the coronary tree, no matter how long, which is planned to be covered with one contiguous length of stent, whether single or overlapped. A bifurcation counts as a single lesion even if the side branch is planned to be treated.

Note: All lesions in a randomized target vessel that are intended to be treated by PCI are designated as target lesions, and at least one target lesion in each randomized target vessel must meet angiographic high-risk inclusion criteria summarized above in 3B). The only exception is for patients who qualify for the trial on the basis of medication-treated diabetes, in which case no target lesion is required to meet angiographic high-risk inclusion criteria.

7. All target lesions intended to be treated by PCI in the target vessel are amenable to OCT-guided PCI (i.e. no lesion-specific angiographic exclusion criteria are present – see Section 5.4.2 below).

Example: If a qualifying angiographic high-risk lesion is in the proximal LAD, and there is a second target lesion in the distal LAD which is a focal lesion not otherwise meeting high-risk criteria, both the proximal LAD and distal LAD lesions must be amenable to OCT (e.g. no excessive tortuosity or calcification precluding delivering the OCT catheter), and each lesion must undergo OCT-guided stenting. Otherwise the vessel should be excluded from randomization.

8. Subject must provide written Informed Consent prior to any study related procedure.

1.8.2 Exclusion Criteria (none may be present)

Clinical exclusion criteria:

1. STEMI ≤24 hours from the onset of ischemic symptoms

2. Creatinine clearance ≤30 ml/min/1.73 m^2 (as calculated by MDRD formula for estimated GFR)[5] and not on dialysis. Note: chronic dialysis dependent patients are eligible for enrolment regardless of creatinine clearance.

3. Hypotension, shock or need for mechanical support or intravenous vasopressors at the time the patient would be undergoing the index procedure.

4. CHF (Killip class ≥2 or NYHA class ≥3)

5. LVEF ≤30% by the most recent imaging test within 3 months prior to procedure. If no LVEF test result within 3 months is available, it must be assessed by echocardiography, multiple gated acquisition (MUGA), magnetic resonance imaging (MRI), ventriculography (LV gram) or other method.

6. Unstable ventricular arrhythmias

7. Inability to take DAPT (both aspirin and a P2Y12 inhibitor) for at least 12 months in the patient presenting with an ACS, or at least 6 months in the patient presenting with stable CAD, unless the

[5] Estimated GFR (ml/min/ 1.73 m^2) = 175 x [SerumCreatinine (umol/L) x 0.0113]$^{-1.154}$ x Age (years)$^{-0.203}$ (x 0.742 if female)

patient is also taking chronic oral anticoagulation in which case a shorter duration of DAPT may be prescribed per local standard of care.

8. Planned major cardiac or non-cardiac surgery within 24 months after the index procedure

Note: Major surgery is any invasive operative procedure in which an extensive resection is performed, e.g. a body cavity is entered, organs are removed, or normal anatomy is altered.

Note: Minor surgery is an operation on the superficial structures of the body or a manipulative procedure that does not involve a serious risk. Planned minor surgery is not excluded.

9. Prior PCI within the target vessel within 12 months

Note: Prior PCI within the target vessel within 12 months is allowed for in-stent restenosis (target lesion is the prior PCI site) if no more than one layer of previously implanted stent is present.

Note: In-stent restenosis involving two or more layers of stent implanted at any time prior to index procedure (i.e. an earlier episode of in-stent restenosis previously treated with a second stent) is excluded.

10. Any planned PCI within the target vessel(s) within 24 months after the study procedure, other than a planned staged intervention in a second randomized target vessel.

*Note: Planned staged interventions must be noted at the time of randomization, and the decision to stage may be modified within 24 hours of completion of the index PCI. See **Section 6.5.3.8** for more details of multi lesion and vessel treatment.*

Note: PCI in non-target vessels is permitted >48 hours after the index procedure.

11. Any prior PCI in a non-target vessel within 24 hours before the study procedure, or within previous 30 days if unsuccessful or complicated.

Note: Patients requiring non-target vessel PCI may be enrolled and the non-target vessel(s) may be treated in the same index procedure as the randomized lesions (in all cases prior to randomization), as long as treatment of the lesion(s) in the non-target vessel is successful and uncomplicated.

Successful and uncomplicated definition for non-target vessel treatment during the index procedure: Angiographic diameter stenosis <10% for all treated non-target lesions, with TIMI III flow in this vessel, without final dissection ≥ NHLBI type B, perforation anytime during the procedure, prolonged chest pain (>5 minutes) or prolonged ST-segment elevation or depression (>5 minutes), or cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation).

12. Subject has known hypersensitivity or contraindication to any of the study drugs (including all P2Y12 inhibitors, one or more components of the study devices, including everolimus, cobalt, chromium, nickel, platinum, tungsten, acrylic and fluoropolymers, or radiocontrast dye that cannot be adequately pre-medicated.

13. Subject has received a solid organ transplant which is functioning or is active on a waiting list for any solid organ transplants with expected transplantation within 24 months.

14. Subject is receiving immunosuppressant therapy or has known immunosuppressive or severe autoimmune disease that requires chronic immunosuppressive therapy (e.g., human immunodeficiency virus, systemic lupus erythematosus, etc.). Note: corticosteroids are not included as immunosuppressant therapy.

15. Subject has previously received or is scheduled to receive radiotherapy to a coronary artery (vascular brachytherapy), or the chest/mediastinum.

16. Subject has a platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3.

17. Subject has a documented or suspected hepatic disorder as defined as cirrhosis or Child-Pugh ≥ Class B.

18. Subject has a history of bleeding diathesis or coagulopathy, or has had a significant gastro-intestinal or significant urinary bleed within the past six months.

19. Subject has had a cerebrovascular accident or transient ischemic neurological attack (TIA) within the past six months, or any prior intracranial bleed, or any permanent neurologic defect, or any known intracranial pathology (e.g., aneurysm, arteriovenous malformation, etc.).

20. Subject has extensive peripheral vascular disease that precludes safe 6 French sheath insertion. Note: femoral arterial disease does not exclude the patient if radial access may be used.

21. Subject has life expectancy <2 years for any non-cardiac cause.

22. Subject is currently participating in another investigational drug or device clinical study that has not yet completed its primary endpoint[6].

23. Pregnant or nursing subjects and those who plan pregnancy in the period up to 2 years following index procedure. Female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to the index procedure per site standard test.

24. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

Angiographic exclusion criteria

1. Syntax score ≥33 as evaluated in **Section 6.5.1**, unless a formal meeting of the Heart Team, including a cardiac surgeon, concludes that PCI is appropriate.

[6] This includes clinical trials of medications and invasive procedures. Questionnaire-based studies, or other studies (regardless of study design) that are non-invasive and do not require medication are allowed. A subject who is taking part in the long-term follow-up phase of a trial, who has completed all medications and invasive procedures per protocol requirements, may continue to participate in that trial.

2. Planned use of any stent <2.5 mm in a target vessel based on visual estimation (note: a smaller stent may be used in a bail-out scenario – e.g. to treat a distal dissection – but its use cannot be planned prior to enrolment)

3. Planned use of a stent or post-dilatation balloon ≥3.75 mm for the target lesion (see inclusion criteria #5 for the one exception to this exclusion criterion)

4. Severe vessel tortuosity or calcification in a target vessel such that it is unlikely that the OCT catheter can be delivered (note: severe vessel calcification is allowed if it is expected that the OCT catheter can be delivered at baseline or after vessel preparation with balloon pre-dilatation or atherectomy)

5. The target vessel has a lesion with DS ≥ 50% that is not planned for treatment at the time of index procedure.

6. The target lesion is in the left main coronary artery

7. The target lesion is in a bypass graft conduit. Note: A native coronary artery may be randomized if a prior bypass graft conduit to the vessel is totally occluded, but not if it is patent.

8. The target lesion is an ostial RCA stenosis

9. The target lesion is a stent thrombosis

10. Planned use of any stent other than Xience in a target lesion

1.9 Enrollment

Subjects are considered enrolled in ILUMIEN IV after signing the Informed Consent. Subjects are considered randomized in the trial after the randomization system has been contacted and a study arm (OCT or angiography guidance) has been assigned. Enrolled subjects not randomized in the trial will be considered screen failures and will not be followed.

1.10 Study Assessments

Baseline/Pre-Randomization Visit:

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, sex, ethnicity and race
- 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
- Physical examination: include subject's height, weight (measurements taken during visit)
- Pregnancy test (negative pregnancy test is required for any female of childbearing potential)
- Serum hemoglobin and creatinine measured within 1 week prior to PCI
- Troponin and/or CK-MB within 48 hours prior to PCI. If abnormal must be repeated either 8-16 hours after the last measurement or drawn from the sheath at the time of the procedure so a curve may be established for peri-procedural MI adjudication. Use of high sensitivity troponin is not recommended.

Note: patients with stable CAD may have the biomarker drawn from the sheath prior to any intervention, and the result does not need to be available prior to treatment.

- 12-lead ECG
- CHF assessment (by Killip class or NYHA class)
- LVEF assessment (if no LVEF test result conducted within 3 months is available). Assessment can be by echocardiography, multiple gated acquisition (MUGA), magnetic resonance imaging (MRI), ventriculography (LV gram) or other method.
- Syntax score for patients with moderately complex 2-vessel disease or any 3-vessel disease. Use the online calculator to determine Syntax score I (http://www.syntaxscore.com). For patients with single vessel disease or simple 2-vessel disease, no calculation is required – record "< 33" for Syntax score.
- Patient Reported Outcome questionnaire (EQ-5D-5L)
- Patients must receive at least 150 mg of oral non-enteric coated aspirin within 12 hours prior to PCI, regardless of prior aspirin use. Intravenous aspirin administration is allowed in geographies where it is standard of care.
- Patients shall receive an appropriate loading dose of an ADP antagonist (clopidogrel, prasugrel or ticagrelor) as per standard of care, preferably within 12 hours prior to, but in all cases no later than 2 hours after PCI. Loading dose of ADP antagonist is not required for subjects receiving chronic treatment of ADP antagonist.

The following considerations apply to subjects having staged procedures, which are described in **Section 6.5.3.8**:

- The protocol required pre-procedure serum creatinine, cardiac enzyme and 12-lead ECG assessments must be repeated for the staged procedure as done for the original index procedure.
- Pre-procedure administration regimen of aspirin and P2Y12 receptor inhibitor (dosage requirements and timing) must be repeated prior to the staged procedure as done for the original index procedure. If the subject has not been discharged between the index and staged procedures, and has received daily aspirin while in hospital, no aspirin reloading is required.

<u>Procedure Visit:</u>

- After the patient meets all inclusion/exclusion criteria in the cardiac catheterization laboratory, the patient is randomized
- PCI is performed according to randomization, with the patient blinded to assignment
- Blinded OCT is performed in the angiography arm at the end of the procedure
- Adverse event assessment

<u>Post-Procedure:</u>

- Troponin level and/or a CK-MB level (CK-MB preferred) drawn at 6-10 hours post PCI. The same biomarkers as those drawn at baseline should be assessed post-PCI.
    - If the results are abnormal (>upper limits of normal), regardless of clinical significance, or if any procedural complications developed (temporary or sustained TIMI flow <III (visually assessed) in any vessel, or dissection ≥ NHLBI type B, or perforation, or prolonged ST-segment elevation or depression (>5 minutes), or cardiac arrest or need for defibrillation or cardioversion or hypotension /heart failure requiring mechanical or intravenous

hemodynamic support or intubation), a second post-PCI troponin level and/or CK-MB level must be drawn at 6-10 hours after the first post-PCI biomarker draw or at discharge.

- In the event of high sensitivity troponin use (which is not recommended), an elevation of <7X ULN in the first (6-10 hr) post-PCI blood draw will not require an additional level, unless any procedural complications developed.

- Creatinine level drawn the calendar day after PCI or before discharge, whichever is earlier.
    - If the subject develops contrast induced nephropathy (defined as an increase in serum creatinine ≥25% or an absolute increase of ≥0.5mg/dl (44.2µmol/L)), regardless of clinical significance, it is recommended that serial creatinine levels be drawn daily until the peak is reached and the creatinine is decreasing.

- Serum hemoglobin drawn the calendar day after PCI or before discharge, whichever is earlier.
    - If the subject develops overt bleeding, or the hemoglobin level has fallen more than 3 g/dL (30 g/L) in the absence of overt bleeding, serial hemoglobin levels must be drawn at least daily until a nadir is reached or the hemoglobin level has stabilized.

- At least one 12-lead ECG must be performed within 24 hours post PCI in all subjects
- Adverse event assessment

Aspirin must be continued indefinitely. DAPT must be continued for at least 6 months in patients with stable CAD and for at least 12 months in patients who presented with acute coronary syndrome unless the patient is also taking chronic oral anticoagulation in which case a shorter duration of DAPT may be prescribed per local standard of care. Post-procedural medication use should not vary according to randomization assignment.

The following considerations apply to subjects having staged procedures:

- The protocol required post-procedure serum creatinine, cardiac enzyme and 12-lead ECG assessments must be repeated for the staged procedure as done for the original index procedure.
- The follow-up regimen of aspirin and P2Y12 receptor inhibitor (dosage requirements and timing) must be maintained following the staged procedure as done for the original index procedure.
- The follow-up period is considered as having begun upon completion of the original index procedure.

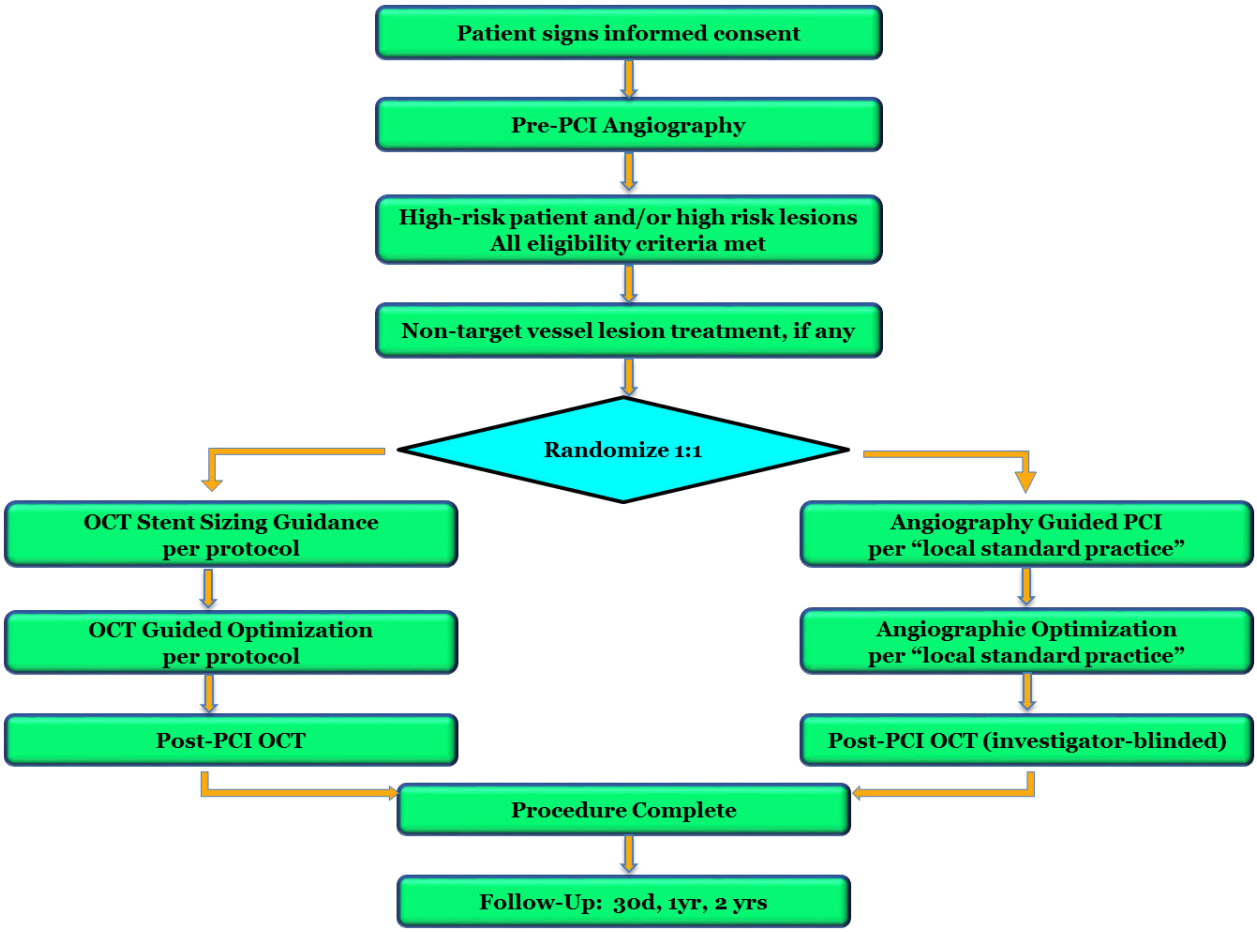
<u>Follow-up Visits (30 days, 1 year, 2 years and unplanned):</u>

- Adverse event assessment, medications, laboratory tests and 12-lead ECGs (if performed) will be collected
- Patient Reported Outcome questionnaires (EQ-5D-5L) administered to subject

1.11 Study leadership

Sponsor	Abbott
Co-Principal Investigator	[redacted]
Co-Principal Investigator	[redacted]
Chairman	[redacted]

1.12 Study Flow Chart



2 Introduction

This document is a clinical investigation plan (CIP) for the ILUMIEN IV clinical investigation. The objective of this clinical investigation is to demonstrate the superiority of an Optical Coherence Tomography (OCT)-guided stent implantation strategy compared to an angiography-guided stent implantation strategy in achieving larger post-PCI lumen dimensions and improving clinical cardiovascular outcomes in patients with high-risk clinical characteristics and/or with high-risk angiographic lesions. In addition, embedded within the ILUMIEN IV protocol is a separate pre-specified powered analysis of XIENCE to be conducted in randomized ILUMIEN IV subjects with in-stent restenosis (ISR). The objective of the analysis is to demonstrate the safety and effectiveness of XIENCE in the treatment of ISR lesions. This is described in further detail in **Appendix F**. This clinical investigation is sponsored by Abbott.

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

3 Background and Justification for Clinical Investigation

Angiography remains the primary method of imaging the coronary artery vasculature to guide clinical decision-making and PCI strategy. However, angiography has a number of well-known limitations; Angiography provides a 2-dimensional representation of a complex 3-dimensional structure. Moreover, the angiogram displays only luminal dimensions and characteristics, without information on vascular remodeling, plaque distribution and eccentricity, or detailed delineation of the extent of disease. The ability of angiography to accurately characterize plaque and tissue types including calcification, lipid and thrombus is poor. Operator assessment of lesion severity both before and after PCI is notoriously inaccurate. Although quantitative coronary angiography is able to reduce intra-observer and inter-observer variability, it is cumbersome and rarely performed (at least in the US), and is unable to overcome other inherent limitations of the technique.[1] Angiography is also suboptimal in its ability to identify post PCI complications such as stent underexpansion or malapposition, residual dissections or thrombus, and tissue prolapse.

These limitations of angiography may be overcome in part by intravascular imaging (IVI), which allows tomographic cross-sectional imaging of the vessel wall. IVI determination of the minimum stent area as well as residual plaque burden and dissections at the stent margins have been shown in numerous studies to be independent predictors of both restenosis and stent thrombosis. Meta-analyses of randomized and registry studies of IVI-guided vs. angiography-guided PCI have suggested that IVUS guidance may decrease restenosis and TVR after treatment with BMS, and restenosis, TVR, stent thrombosis, and death after treatment with DES.[2,3] The large-scale ADAPT-DES study demonstrated that IVI guidance leads to larger stent expansion and use of longer stents, with associated reductions in stent thrombosis, MI, TLR and cardiac death.[4] The primary modality of IVI used in these studies was intravascular ultrasound (IVUS).

Despite its advantages IVUS has some important limitations. Due to limited axial resolution (150-200 µm), IVUS is unable to image behind calcium, discriminate thrombus and other plaque subtypes, assess fibrous cap thickness with resolution sufficient to identify vulnerable plaque, and is limited by the photoacoustic properties of sound and therefore requires slow pullback.

Optical coherence tomography (OCT) is a newer intravascular imaging modality that provides high-resolution (10-20 µm) cross-sectional images of plaque microarchitecture, stent placement and size and strut coverage. However, despite the greatly improved resolution of OCT compared to IVUS, the penetration depth of OCT is limited, and as such the full thickness of the vascular wall may not be visible in the presence of lipidic or calcified plaque. As a result, the dogma became that certain measurements that require visualization of the external elastic lamina (EEL), including vessel area and plaque burden, which are used by IVUS operators to optimally size stents, could not be reliably assessed with OCT. Consequently, lumen-based sizing for OCT was adopted and guidance incorporated into clinical investigations of OCT leading to a disadvantage compared to EEL-based or mid-wall-based guidance by IVUS (**Table 1**). Furthermore, using identical sizing OCT still yields smaller minimal stent area (MSA) compared to IVUS where dimensions are established to be over-estimated by ≈10%. As a result, OCT is disadvantaged in two ways to achieve comparable stent sizes to IVUS. We therefore developed an algorithm for OCT to optimize coronary stent implantation based on sizing of the vessel at the proximal and distal reference using the EEL. This algorithm was tested in the ILUMIEN III: OPTIMIZE PCI study which randomized 450 patients to IVUS-guided, OCT-guided, or angiography-guided PCI. The ILUMIEN III trial found that an EEL-based stent optimization strategy for OCT was safe and resulted in similar MSA to that of IVUS-guided PCI with a trend toward larger MSA compared to angiography guidance, and less untreated PCI complications.

Table 1. Final Minimum Stent Area Outcomes in Imaging Guided PCI Trials. Data are shown as mean ± standard deviation or median [1st and 3rd interquartile range]. N: number, MSA: minimal stent area. EEL: external elastic lamina.

Study	OCT (n)	Control (n)	Reference measurement		MSA (mm^2)		P	Largest MSA
Wijns[5]	137	65	OCT Lumen	Angio Lumen	6.1±2.5	5.0±2.0	0.004	Angio
Habrara[6]	35	36	OCT Lumen	IVUS EEL	6.1±2.2	7.1±2.1	0.04	IVUS
Maehara[7]	286	286	OCT Lumen	IVUS EEL	5.0 [3.9,6.4]	5.5 [4.4,7.0]	<0.0001	IVUS
Otake [8]	50	50	OCT Lumen	IVUS EEL	5.3±1.6	6.1±2.3	0.088	IVUS
Ali[9]	158	146	OCT EEL	IVUS EEL	5.8 [4.5,7.3]	5.9 [4.7,7.8]	0.42	Equal

Due to its high resolution and ability to accurately optimize and identify suboptimal results of stent implantation, it is plausible that the use of this OCT-guided algorithm may improve clinical outcome of stent implantation However, due to cost and catheterization laboratory workflow it may not be feasible and cost effective to perform OCT-guided PCI in every lesion. In the present study we aim to compare the outcomes of OCT-guided stent implantation to those achieved with angiography guided stent implantation, specifically among in high-clinical-risk patients or high-angiographic-risk lesions.

4 Study Devices

4.1 Identification and Description of Study Devices

4.1.1 Identification

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.1.2 Device Description and Intended Purpose

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.1.3 Device Handling and Storage

Sponsor requires all study devices be stored according to the labeling and Instructions for Use.

4.2 Device Accountability

ILUMIEN IV is an investigation using market released medical devices and device accountability is not required.

5 Clinical Investigation Design

5.1 Clinical Investigation Design

This is a prospective, single-blind clinical investigation randomizing subjects to OCT-guided coronary stent implantation vs. angiography-guided coronary stent implantation in a 1:1 ratio. The clinical investigation will be conducted at approximately 125 centers in North America (US and Canada), Europe, Middle East and Asia-Pacific. Up to 3656 subjects will be enrolled in the clinical investigation. No site may enroll more than 15% of the total subjects.

There are two powered primary endpoints of the study. The primary imaging endpoint is the acute post-procedural MSA (per target lesion basis) by OCT-guided-PCI compared to angiography-guided PCI. The MSA is an appropriate primary endpoint as it is the most consistent and strongest parameter to predict clinical outcomes.[10-18] In the present study, after 1600 randomized subjects are enrolled with procedure completed, the primary endpoint of MSA will be tested to compare OCT-guided and angiography-guided arms. If significantly larger MSA in OCT-guided arm is demonstrated, the trial will continue enrolling subjects. Otherwise the trial may be terminated for futility at the discretion of the sponsor.

The primary clinical endpoint is target vessel failure (TVF), the time-to-first event rate of the composite outcome of cardiac death, target vessel myocardial infarction (TV-MI) (per primary protocol definition [see Appendix B]), or ischemia-driven target vessel revascularization (ID-TVR), assessed at 2 years.

Due to its high resolution and ability to support an optimal strategy planning for complex PCI as well as accurately optimize and identify suboptimal results of stent implantation, it is hypothesized that OCT-guided PCI will be superior to angiography-guided PCI for both the achieved MSA and rates of TVF. For the greatest benefit to be achieved, OCT will be performed in the present study according to a slightly modified version of the algorithm used in ILUMIEN III:OPTIMIZE PCI.[19]

All subjects participating in this clinical investigation will be followed for 2 years. [redacted]

[redacted]

5.1.1 Blinding

This is a prospective, randomized, single-blind clinical investigation. Subjects will be blinded to their treatment assignment and the study site personnel will be trained not to disclose the treatment assignment to the subject. In addition to standard procedural sedation, headphones will be worn by the patient during the procedure to reduce the possibility of unblinding. Patients who refuse to wear headphones may not be randomized into the study. Additionally, blinded site personnel, not present at the index procedure, will conduct the clinical follow-up and they will be provided with a standard follow-up interview in order to reduce bias and maintain subject blinding. Subject blinding must be maintained until the completion of the trial.

The physician performing the procedure will not be blinded to the assigned treatment. Thus, if clinical follow-up with a study physician is deemed necessary at the protocol required follow-up time points, a different physician (or designee) than the one who implanted the device(s) must conduct the follow-up clinical visits in order to maintain subject blinding. Similarly, follow-up visits with research personnel must be conducted by different persons than those who were unblinded during the index hospitalization. Site personnel will be adequately trained such that the physician (or designee) conducting the clinical follow-up is adequately blinded to the treatment received by the subject. For unscheduled visits, subjects may see the physician who performed the procedure. The treating physician should prevent unblinding of the subject when they conduct any non-protocol related visits. In addition, any records to which the patient may have direct access should not refer to details of intravascular imaging or use other revealing language, to maintain the blind. The only exception to these requirements is if the hospital billing department does not allow this practice. Sites will be provided with a blinding guidance document that will instruct the sites on how to maintain blinding at the clinical sites.

The Clinical Events Committee (CEC) may not be blinded to the randomization assignment in all patients. The angiographic core laboratories may not be blinded to treatment strategy in all patients. The Data Safety Monitoring Board (DSMB) will be blinded to the subject's randomization. Independent statisticians will generate blinded tables for review by the DSMB. The DSMB may request unblinded data if a safety signal is observed.

Sponsor personnel that will be unblinded will be the independent biostatisticians involved in generating and verifying the randomization code, key Clinical Science and Operations, Clinical Safety Monitors, Site Monitors, Clinical Data Management, Electronic Database Programmer, Inventory Management staff, and Clinical Information System (IS) personnel working on the trial. Restricted access of blinded personnel to the clinical database will be maintained until unblinding of the study for analysis of the primary clinical outcome at 2 years, described below in **Section 5.3.1**.

5.2 Objectives

5.2.1 Primary Objective

The objective of this clinical investigation is to demonstrate the superiority of an Optical Coherence Tomography (OCT)-guided stent implantation strategy compared to an angiography-guided stent implantation strategy in achieving larger post-PCI lumen dimensions and improving clinical cardiovascular outcomes in patients with high-risk clinical characteristics and/or with high-risk angiographic lesions.

5.3 Endpoints

There are two powered primary endpoints, one powered major secondary endpoint and multiple descriptive non-powered secondary endpoints in this clinical investigation. Both primary endpoints must be positive for the investigation to be considered positive.

5.3.1 Primary Endpoints

1. Imaging Outcome (powered): Minimal stent area (MSA), continuous measure

   Final Post-PCI MSA (per target lesion basis) assessed by OCT in each randomized arm, measured at an independent OCT core laboratory blinded to imaging modality assignment.

2. Clinical outcome (powered): Target vessel failure (TVF)

   Time-to-first event rate of the composite outcome of cardiac death, target vessel myocardial infarction (TV-MI) (per primary protocol definition [see Appendix B]), or ischemia-driven target vessel revascularization (ID-TVR), assessed at 2 years.

5.3.2 Major Secondary Endpoint

1) Target vessel failure (TVF) excluding periprocedural MI.

   Time-to-first event rate of the composite outcome of cardiac death, target vessel-related spontaneous myocardial infarction, or ischemia-driven target vessel revascularization (ID-TVR), assessed at 2 years.

5.3.3 Non-Powered Secondary Endpoints

Procedural outcomes, additional procedural and clinical endpoints, patient reported outcomes (PRO) and cost-effectiveness measures listed below

Procedural outcomes

OCT-defined (OCT core laboratory assessed). Subjects in the angiography-guided arm will undergo a post-PCI OCT run, blinded to the operator. Assessed per target lesion.

1) Stent expansion. Stent expansion is defined by the MSA achieved in the proximal and distal stented segments relative to their respective reference lumen areas. The stent length is divided into 2 equal segments (proximal and distal) except for lesions containing a bifurcation (visually estimated side branch ≥2.5 mm). When there is a bifurcation present, rather than splitting the stent into two halves, the division occurs at the proximal most side branch.

   - Acceptable stent expansion (categorical variable): The MSA of the proximal segment is ≥90% of the proximal reference lumen area and the MSA of the distal segment is ≥90% of the distal reference lumen area.

   - Unacceptable stent expansion (categorical variable): The MSA of the proximal segment is <90% of the proximal reference lumen area, and/or the MSA of the distal segment is <90% of the distal reference lumen area.

   In case either segment (proximal or distal) of the stent meets criteria for unacceptable stent expansion, the stent is considered to have unacceptable stent expansion. Both segments of the stent must meet acceptable stent expansion criteria to be considered acceptable.

   In case a respective reference segment cannot be measured the determination will be made with only one of the two reference (proximal or distal) segments.

Note: If acceptable stent expansion (by operator assessment) is not achieved in either the distal or proximal segments of the stent in the OCT-guided arm according to the Post-PCI OCT, further post-stent expansion with higher pressures and/or larger balloons must be performed per protocol if the POST-PCI OCT EEL measurements now suggest a larger balloon be used. See ***Section 6.5.3.7*** *for more details.*

- Post-PCI stent expansion (%) (continuous variable): The MSA divided by the average of proximal and distal reference lumen areas x 100.

2) Mean stent expansion (%) (continuous variable): The mean stent area (stent volume/analysed stent length) divided by the average of proximal and distal reference lumen areas x 100.

3) Intra-stent plaque protrusion and thrombus

Defined as a mass attached to the luminal surface or floating within the lumen, meeting the following criteria: Protrusion/thrombus is defined as any intraluminal mass protruding at least 0.2 mm within the luminal edge of a stent strut, and will be further classified as Major and Minor:

- Major: Protrusion area/Stent area at site of tissue protrusion ≥10% and the minimal intrastent flow area (MSA – protrusion area) is unacceptable (<90% of respective proximal or distal reference area
- Minor: Protrusion area/Stent area at site of tissue protrusion is <10%, or is ≥10% but the minimal intraluminal flow area (MSA – protrusion area) is acceptable (≥90% of respective proximal or distal reference area

Note: It is recommended that if protrusion is detected by operator assessment in the OCT-guided arm during the procedure and meets the criteria for major protrusion, then thrombus aspiration, further high-pressure balloon inflation and/or an additional stent be considered.

4) Untreated reference segment disease

Defined as focal disease with untreated MLA <4.5 mm^2 within 5 mm from the proximal and/or distal stent edges.

Sub-classified by the amount of untreated lipid plaque, divided into 3 grades:

i. Low (≤90° of lipid arc)

ii. Medium (>90°-<180° of lipid arc)

iii. High (≥180° of lipid arc)

Note: If untreated reference segment disease with an MLA <4.5 mm^2 is detected by operator assessment in either the proximal reference (inflow disease) or distal reference (outflow disease) segment lumen in the OCT-guided arm, an additional stent must be placed to treat it, unless there are anatomic reasons that the disease should not be covered (e.g. diffuse distal disease or significant vessel tapering, etc.) (Figures 1a-b).

5) Edge dissections

Edge dissections will be tabulated as:

i. Major (%): ≥60 degrees of the circumference of the vessel at site of dissection and ≥3 mm in length

ii. Minor (%): any visible edge dissection <60 degrees of the circumference of the vessel or <3 mm in length

Edge dissections will be further classified as:

i. Intimal (limited to the intima layer, i.e. not extending beyond the internal elastic lamina)

ii. Medial (extending into the media layer)

iii. Adventitial (extending through the external elastic membrane/lamina)

Note: If a major edge dissection is detected by operator assessment in the OCT-guided arm, it is recommended that an additional stent be placed to cover the dissected segment, particularly if the site of dissection is at the distal stent edge.

6) Stent Malapposition

Defined as frequency (%) of incompletely apposed stent struts (defined as stent struts clearly separated from the vessel wall (lumen border/plaque surface) without any tissue behind the struts with a distance from the adjacent intima of ≥0.2 mm and not associated with any side branch).

Malapposition will be further classified as:

- Major: if associated with unacceptable stent expansion (as defined above)
- Minor: if associated with acceptable stent expansion (as defined above)

Note: If malapposition is detected by operator assessment during the procedure in the OCT-guided arm and meets the criteria for major malapposition (i.e. malapposition associated with unacceptable stent expansion), further stent expansion must be performed. The degree of stent underexpansion (acceptable or unacceptable) should guide the intervention rather than amount of malapposition.

Stent Malapposition will be tabulated as:

i. Major (%)

ii. Minor (%)

iii. All (Major and Minor) (%)

7) Border detection (angiography arm post-PCI only, blinded to investigator)

The visibility of the vessel external elastic lamina (EEL) border by OCT will be evaluated at both reference sites (proximal and distal) and the MSA, after intervention and then classified into 3 grades:

i. Good: ≥75% (270°) of visible circumference

ii. Moderate: ≥50% (180°) - <75% (270°) of visible circumference

iii. Poor: <50% (180°) of visible circumference

8) Intra-stent lumen area (intra-stent flow area)

Defined as stent area minus any protrusion as defined above in secondary endpoint 3) (Intra-stent plaque protrusion and thrombus).

9) Effective lumen area (total flow area)

Defined as intra-stent lumen area plus any area of malapposition between the stent and the vessel wall (lumen border/plaque border).

Additional Procedural and Clinical Endpoints

10) Angiographic Endpoints (QCA). (Angiographic core laboratory assessed). Assessed per target lesion.

i. Final (post-PCI) minimal lumen diameter
ii. Final (post-PCI) percent diameter stenosis
iii. Acute lumen gain post-intervention
iv. Maximum device size (stent or post-dilatation balloon)/reference vessel diameter ratio
v. Post-PCI target vessel TIMI flow rate
vi. Angiographic complications – worst (anytime during the procedure) and final (post PCI and all imaging) - Angiographic dissection ≥ NHLBI type B, perforations (Ellis classification), intra-procedural thrombotic events (including slow-flow, no-reflow, side branch closure, distal embolization, and intra-procedural stent thrombosis, as per the standard angiographic core laboratory definitions

11) Device Usage Endpoints (site reported; assessed per subject):

i. Total stent length
ii. Total number of stents
iii. Maximal stent size
iv. Post dilatation (yes/no)
v. Total number of post-dilatation balloons
vi. Maximal post-dilatation balloon size
vii. Maximal device size (stent or post-dilatation balloon)
viii. Maximum inflation pressure (atm.; stent or post-dilatation balloon)

12) Procedure time (first wire insertion to guide catheter removal), fluoroscopy time, radiation exposure

13) Contrast use; contrast induced nephropathy (defined as serum creatinine rise >25% or absolute increase >0.5 mg/dL (44.2µmol/L)); need for renal replacement therapy

14) Procedural success (must be present in all treated lesions and vessels):

Defined as A) angiographic core laboratory-assessed final (post-PCI) lesion angiographic diameter stenosis <30% and target vessel TIMI III flow without any of the angiographic complications listed in 10(vi) above; plus B) the absence of site-assessed prolonged ST-segment elevation or depression (>30 minutes), cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation, or procedural death.

15) Procedural complications

Defined as A) angiographic core laboratory-assessed complications listed in 10(vi) above occurring anytime during the procedure; or B) site-assessed prolonged ST-segment

elevation or depression (>30 minutes), cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation, or procedural death.

16) OCT performance success (site reported) (OCT arm only):

    OCT imaging performed both pre- and post-PCI

17) OCT imaging-related procedural complications (CEC adjudicated)

Any procedural complications (e.g. angiographic dissection, perforation, thrombus, acute closure, etc.) requiring any active intervention (e.g. prolonged balloon inflations, additional stent implantation, pericardiocentesis, intubation, hemodynamic support or pressors, defibrillation or cardioversion) or death adjudicated by the CEC as definitely or likely attributable to the physical performance of OCT-imaging (e.g. passing the catheter through the vasculature or stent, or injecting contrast to clear the blood for imaging). For this definition, adverse events that arise due to changes in PCI strategy as the result of OCT findings are NOT considered OCT imaging-related procedural complications.

18) Additional interventions on the basis of the pre-PCI or post-stent OCT-imaging run that would not have been performed based on angiographic guidance alone (site reported; assessed per subject; OCT Arm Only):

    i. Use of larger balloon
    ii. Use of higher inflation pressures
    iii. Use of additional balloons
    iv. Use of additional stent(s)
    v. Performance of atherectomy
    vi. Other interventions

Reason(s) for additional interventions will be documented by the site (e.g. more calcium than anticipated, greater stent under-expansion than appreciated angiographically, greater malapposition than appreciated angiographically, greater tissue protrusion or thrombus burden than appreciated angiographically, more severe edge dissection than appreciated angiographically, residual reference segment disease not appreciated angiographically, other)

Clinical outcomes at 30 days, 1 year and 2 years (unless otherwise noted)

19) Target lesion failure (TLF; cardiac death, TV-MI or ischemia-driven target lesion revascularization (ID-TLR)

20) All-cause mortality

21) Cardiac and non-cardiac mortality

22) All MI

23) TV-MI, non-TV-MI and indeterminate vessel MI

24) Periprocedural MI and non-periprocedural MI

25) All revascularization

26) ID-revascularization and non-ID-revascularization

27) ID-TVR, ID-TLR, ID-non-TLR TVR, and ID-non-TVR

28) Definite, probable and definite/probable stent thrombosis (ARC definition)

29) Relationship between immediate post-procedure OCT parameters (e.g. MSA, procedural success, malapposition, dissection, protrusion, etc.) and 2-year endpoint rates (e.g. TVF, TLF, all-cause mortality, cardiac death, TV-MI, all MI, , ID-TLR, ID-TVR, and stent thrombosis)

30) TVF excluding periprocedural MI (i.e. the composite of cardiac death, target vessel-related spontaneous MI, or ID-TVR) (at 30 days and 1 year)

In addition, the following outcomes using the SCAI definition of periprocedural MI[9] will be reported as sensitivity analyses at 30 days, 1 year and 2 years:

31) TV-MI$_{SCAI}$ (periprocedural MI by SCAI definition and spontaneous MI by protocol definition)

32) Periprocedural MI$_{SCAI}$ (by SCAI definition)

33) All MI$_{SCAI}$ (periprocedural MI by SCAI definition and spontaneous MI by protocol definition)

34) TVF$_{SCAI}$; the composite of cardiac death, TV-MI$_{SCAI}$ or ID-TVR

Patient Reported Outcomes (PRO)

Patient Reported Outcome questionnaires will be incorporated into this study to provide a complementary evaluation of the effectiveness of OCT-guided stent implantation. The following instruments will be administered during this study in hospital (required at baseline, optional post-procedure), and at 30 day, 12 month and 24 month follow-up:

- EuroQoL 5D (EQ-5D-5L) survey to assess overall health status

Cost-effectiveness

Cost per quality adjusted life year (QALY) and TVF event prevented by OCT-guidance to be determined using standardized methods[10].

5.4 Study Population

The intended population for this clinical investigation is patients over the age of 18 years that are either high clinical-risk or have high angiographic-risk lesion characteristics undergoing stent implantation for coronary artery disease.

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

[9] Moussa ID et al. Consideration of a New Definition of Clinically Relevant Myocardial Infarction After Coronary Revascularization: An Expert Consensus Document From the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol. 2013 October 22; 62(17): 1563–1570.
[10] Eisenberg J. Clinical economics: A guide to the economic analysis of clinical practices. JAMA 1989; 262:2879-86.

be done but after written informed consent is obtained. Patients 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.

5.4.1 Inclusion Criteria (all must be present)

1. Subject must be at least 18 years of age.

2. Subject must have evidence of myocardial ischemia (e.g., stable angina, silent ischemia (ischemia in the absence of chest pain or other anginal equivalents), unstable angina, or acute myocardial infarction) suitable for elective PCI.

3. Patients undergoing planned XIENCE stent implantation during a clinically indicated PCI procedure meeting one or more of the following criteria:

A) High clinical-risk, defined as;

i. Medication-treated diabetes mellitus, AND/OR

B) High angiographic-risk lesion(s), with at least one target lesion in each target vessel planned for randomization meeting at least one of the following criteria;

i. Target lesion is the culprit lesion responsible for either:
   - NSTEMI, defined as a clinical syndrome consistent with an acute coronary syndrome and a minimum troponin of 1 ng/dL (may or may not have returned to normal), OR
   - STEMI >24 hours from the onset of ischemic symptoms

ii. long or multiple lesions (defined as intended total stent length in any single target vessel ≥28 mm),

Note: For a long target lesion, this would permit treatment by a single long stent or overlapping stents.

Note: For up to two target lesions located in a single target vessel and treated with non-overlapping stents, they may be located in a continuous vessel or split up between a main vessel and a side branch.

iii. bifurcation intended to be treated with 2 planned stents (i.e. in both the main branch and side branch), and where the planned side branch stent is ≥ 2.5 mm in diameter by angiographic visual estimation.

iv. angiographic severe calcification (defined as angiographically visible calcification on both sides of the vessel wall in the absence of cardiac motion),

v. chronic total occlusion (CTO) (enrolment and randomization in this case performed only after successful antegrade wire escalation crossing and pre-dilatation)

vi. in-stent restenosis of diffuse or multi-focal pattern. Lesion must be at or within the existing stent margin(s) and have angiographically visually-assessed DS ≥70% or DS ≥50% with non-invasive or invasive evidence of ischemia

4. All target lesions (those lesions to be randomized) must have a visually estimated or quantitatively assessed %DS of either ≥70%, or ≥50% plus one or more of the following: an abnormal functional test (e.g. fractional flow reserve, stress test) signifying ischemia in the distribution of the target lesion(s) or biomarker positive ACS with plaque disruption or thrombus.

Note: For purposes of study eligibility, a minimum troponin of 1 ng/dL at the time of screening will be considered biomarker positive.

5. All target lesions must be planned for treatment with only ≥2.5 mm and ≤3.5 mm stents and post-dilatation balloons based on pre-PCI angiographic visual estimation..

6. No more than 2 target lesions requiring PCI are present in any single vessel., and no more than 2 target vessels are allowed. Thus, up to 4 randomized target lesions per patient in a maximum of 2 target vessels are allowed, including branches. The intended target lesions will be declared just prior to randomization.

Note: A lesion is defined as any segment(s) of the coronary tree, no matter how long, which is planned to be covered with one contiguous length of stent, whether single or overlapped. A bifurcation counts as a single lesion even if the side branch is planned to be treated.

Note: All lesions in a randomized target vessel that are intended to be treated by PCI are designated as target lesions, and at least one target lesion in each randomized target vessel must meet angiographic high-risk inclusion criteria summarized above in 3B). The only exception is for patients who qualify for the trial on the basis of medication-treated diabetes, in which case no target lesion is required to meet angiographic high-risk inclusion criteria.

7. All target lesions intended to be treated by PCI in the target vessel are amenable to OCT-guided PCI (i.e. no lesion-specific angiographic exclusion criteria are present – see Section 5.4.2 below).

Example: If a qualifying angiographic high-risk lesion is in the proximal LAD, and there is a second target lesion in the distal LAD which is a focal lesion not otherwise meeting high-risk criteria, both the proximal LAD and distal LAD lesions must be amenable to OCT (e.g. no excessive tortuosity or calcification precluding delivering the OCT catheter), and each lesion must undergo OCT-guided stenting. Otherwise the vessel should be excluded from randomization.

8. Subject must provide written Informed Consent prior to any study related procedure.

5.4.2 Exclusion Criteria (none may be present)

Clinical exclusion criteria:

1. STEMI ≤24 hours from the onset of ischemic symptoms

2. Creatinine clearance ≤30 ml/min/1.73 m^2 (as calculated by MDRD formula for estimated GFR)[11] and not on dialysis. Note: chronic dialysis dependent patients are eligible for enrolment regardless of creatinine clearance.

3. Hypotension, shock or need for mechanical support or intravenous vasopressors at the time the patient would be undergoing the index procedure.

4. CHF (Killip class ≥2 or NYHA class ≥3)

5. LVEF ≤30% by the most recent imaging test within 3 months prior to procedure. If no LVEF test result within 3 months is available, it must be assessed by echocardiography, multiple gated acquisition (MUGA), magnetic resonance imaging (MRI), ventriculography (LV gram) or other method.

6. Unstable ventricular arrhythmias

7. Inability to take DAPT (both aspirin and a P2Y12 inhibitor) for at least 12 months in the patient presenting with an ACS, or at least 6 months in the patient presenting with stable CAD, unless the patient is also taking chronic oral anticoagulation in which case a shorter duration of DAPT may be prescribed per local standard of care.

8. Planned major cardiac or non-cardiac surgery within 24 months after the index procedure

   Note: Major surgery is any invasive operative procedure in which an extensive resection is performed, e.g. a body cavity is entered, organs are removed, or normal anatomy is altered.

   Note: Minor surgery is an operation on the superficial structures of the body or a manipulative procedure that does not involve a serious risk. Planned minor surgery is not excluded.

9. Prior PCI within the target vessel within 12 months

   Note: Prior PCI within the target vessel within 12 months is allowed for in-stent restenosis (target lesion is the prior PCI site) if no more than one layer of previously implanted stent is present.

   Note: In-stent restenosis involving two or more layers of stent implanted at any time prior to index procedure (i.e. an earlier episode of in-stent restenosis previously treated with a second stent) is excluded.

[11] Estimated GFR (ml/min/ 1.73 m^2) = 175 x [SerumCreatinine (umol/L) x 0.0113]$^{-1.154}$ x Age (years)$^{-0.203}$ (x 0.742 if female)

10. Any planned PCI within the target vessel(s) within 24 months after the study procedure, other than a planned staged intervention in a second randomized target vessel.

Note: Planned staged interventions must be noted at the time of randomization, and the decision to stage may be modified within 24 hours of completion of the index PCI. See ***Section 6.5.3.8*** *for more details of multi lesion and vessel treatment.*

Note: PCI in non-target vessels is permitted >48 hours after the index procedure.

11. Any prior PCI in a non-target vessel within 24 hours before the study procedure, or within previous 30 days if unsuccessful or complicated.

Note: Patients requiring non-target vessel PCI may be enrolled and the non-target vessel(s) may be treated in the same index procedure as the randomized lesions (in all cases prior to randomization), as long as treatment of the lesion(s) in the non-target vessel is successful and uncomplicated.

Successful and uncomplicated definition for non-target vessel treatment during the index procedure: Angiographic diameter stenosis <10% for all treated non-target lesions, with TIMI III flow in this vessel, without final dissection ≥ NHLBI type B, perforation anytime during the procedure, prolonged chest pain (>5 minutes) or prolonged ST-segment elevation or depression (>5 minutes), or cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation).

12. Subject has known hypersensitivity or contraindication to any of the study drugs (including all P2Y12 inhibitors, one or more components of the study devices, including everolimus, cobalt, chromium, nickel, platinum, tungsten, acrylic and fluoropolymers, or radiocontrast dye that cannot be adequately pre-medicated.

13. Subject has received a solid organ transplant which is functioning or is active on a waiting list for any solid organ transplants with expected transplantation within 24 months.

14. Subject is receiving immunosuppressant therapy or has known immunosuppressive or severe autoimmune disease that requires chronic immunosuppressive therapy (e.g., human immunodeficiency virus, systemic lupus erythematosus, etc.). Note: corticosteroids are not included as immunosuppressant therapy.

15. Subject has previously received or is scheduled to receive radiotherapy to a coronary artery (vascular brachytherapy), or the chest/mediastinum.

16. Subject has a platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3.

17. Subject has a documented or suspected hepatic disorder as defined as cirrhosis or Child-Pugh ≥ Class B.

18. Subject has a history of bleeding diathesis or coagulopathy, or has had a significant gastro-intestinal or significant urinary bleed within the past six months.

19. Subject has had a cerebrovascular accident or transient ischemic neurological attack (TIA) within the past six months, or any prior intracranial bleed, or any permanent neurologic defect, or any known intracranial pathology (e.g., aneurysm, arteriovenous malformation, etc.).

20. Subject has extensive peripheral vascular disease that precludes safe 6 French sheath insertion. Note: femoral arterial disease does not exclude the patient if radial access may be used.

21. Subject has life expectancy <2 years for any non-cardiac cause.

22. Subject is currently participating in another investigational drug or device clinical study that has not yet completed its primary endpoint[12].

23. Pregnant or nursing subjects and those who plan pregnancy in the period up to 2 years following index procedure. Female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to the index procedure per site standard test.

24. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

Angiographic exclusion criteria

1. Syntax score ≥33 as evaluated in **Section 6.5.1**, unless a formal meeting of the Heart Team, including a cardiac surgeon, concludes that PCI is appropriate.

2. Planned use of any stent <2.5 mm in a randomized vessel based on visual estimation (note: a smaller stent may be used in a bail-out scenario – e.g. to treat a distal dissection – but its use cannot be planned prior to enrolment)

3. Planned use of a stent or post-dilatation balloon ≥3.75 mm for the randomized target lesion (see inclusion criteria #5 for the one exception to this exclusion criterion)

4. Severe vessel tortuosity or calcification in a randomized target vessel such that it is unlikely that the OCT catheter can be delivered (note: severe vessel calcification is allowed if it is expected that the OCT catheter can be delivered at baseline or after vessel preparation with balloon pre-dilatation or atherectomy)

5. The target vessel has a lesion with DS ≥ 50% that is not planned for treatment at the time of index procedure

6. The randomized target lesion is in the left main coronary artery

[12] This includes clinical trials of medications and invasive procedures. Questionnaire-based studies, or other studies (regardless of study design) that are non-invasive and do not require medication are allowed. A subject who is taking part in the long-term follow-up phase of a trial, who has completed all medications and invasive procedures per protocol requirements, may continue to participate in that trial.

7. The randomized target lesion is in a bypass graft conduit. Note: A native coronary artery may be randomized if a prior bypass graft conduit to the vessel is totally occluded, but not if it is patent.

8. The randomized target lesion is an ostial RCA stenosis

9. The randomized target lesion is a stent thrombosis

10. Planned use of any stent other than Xience in a randomized target lesion

5.4.3 Enrollment of Medicare Beneficiaries

This clinical trial will enroll appropriate Medicare beneficiaries that qualify based on the inclusion and exclusion criteria set forth in the trial. This IDE clinical trial adheres to all standards of Medicare coverage requirements set forth by the IDE and clinical trial coverage policies of the Center for Medicare and Medicare Services (CMS). Section 8, Risks and Benefits, describes how all enrolled subjects, including Medicare beneficiaries, may be affected by this investigation.

Subjects enrolled in the clinical trial are expected to be consistent with the Medicare population based on demographic characteristics and cardiovascular risk factors; therefore, the clinical trial results are expected to be generalizable to the Medicare population.

6 Procedures

6.1 Overview

Operator experience and performance in the randomized trial.
Operators participating in this study will be those who have performed at least 50 lifetime OCT-guided stent procedures.
As described in **Section 6.4**, each operator will perform up to 3 roll-in subjects prior to randomization. Roll-in patients must meet all inclusion and exclusion criteria as randomized patients. The procedural results, angiograms and OCT technique and data for each roll-in case will be reviewed by the OCT core laboratory director. When it is agreed that the operator has full understanding of the OCT-guidance protocol, the roll-in requirement for that operator will stop and randomization may proceed. If after 3 roll-in cases the operator is still not complying with the OCT-guidance protocol, that operator will not be permitted to randomize within the trial.

For all patients, each clinical site should transmit the angiographic and OCT images to the core laboratories within 48 hours of the case being completed.

For patients randomized to OCT-guidance, the OCT core laboratory director will review each case to determine whether the protocol for OCT-stent guidance was followed, including but not limited to:

- Was the protocol followed to obtain an acceptable MSA?
- Were any major inaccuracies in dimensional or other OCT measurements present?
- Did the operator act appropriately on the final OCT?
- Were any other major protocol violations detected?

For patients randomized to angiography-guidance, the OCT core laboratory director will review each case to determine that no additional interventions were performed after the blinded OCT imaging (which would represent a protocol violation), and that the quality of this blinded OCT run was acceptable.

The OCT core laboratory director may consult the trial Principal Investigator, and/or contact the sites for additional data if necessary to make these assessments. The OCT core laboratory director will send a screening report back to the sites within 72 hours of receipt of the images detailing if any major or minor protocol violations were present. If any major protocol violations were present, the operator may be put on "clinical hold" and asked not to randomize further until further training has been performed. If an operator has 3 such major protocol violations, he/she may be asked to withdraw from the study (although all randomized patients will remain in the study by intention to treat).

Patients undergoing coronary angiography in whom possible or definite PCI with intent to implant a stent will be asked to participate in the study. Patient demographics and a medical history are required for all patients. All patients must have a baseline 12-lead ECG prior to angiography, and a baseline troponin and/or CK-MB level within 48 hours prior to PCI – this may be drawn from the vascular sheath prior to PCI in patients with stable coronary artery disease. Patients also must have a baseline serum creatinine and hemoglobin measured within 1 week prior to PCI. Location of vascular access (whether radial or femoral) is per local site discretion, as is sheath size, although at least a 6F sheath must be used. After the informed consent for the study is signed by the patient, angiography will be performed. At least 100 µg of IC nitroglycerin or appropriate dosage of IC isosorbide dinitrate must be administered prior to angiography. All patients must be pre-treated with at least 150 mg of oral non-enteric coated aspirin within 12 hours prior to PCI regardless of prior aspirin use. Intravenous aspirin administration is allowed in geographies where it is standard of care. All patients should receive a loading dose of an ADP antagonist (clopidogrel, prasugrel or ticagrelor) as per standard of care, preferably within 12 hours prior to, but in all cases no later than 2 hours post PCI. Loading dose of ADP antagonist is not required for subjects receiving chronic treatment of ADP antagonist.

Following angiography (and successful and uncomplicated treatment of any non-target vessel lesions, if present), eligible patients will be randomized in a 1:1 ratio to OCT-guided stent implantation or angiography-guided stent implantation. An exception is if a randomized target lesion will be a CTO, in which case randomization is performed only following successful crossing and pre-dilatation, such that the lesion is confirmed as amenable to OCT guidance. If the CTO is not successfully crossed and dilated, the patient may not be randomized). Among the OCT-guided group, coronary stenting will be performed according to the OCT-sizing and optimization algorithm, while in the angiography-guided PCI group, coronary stenting will be performed as per local standard of care. All patients must have a post-PCI 12-lead ECG and measurement of at least 1 cardiac biomarker level as described below.

Follow up visits will be scheduled at 1, 12 and 24 months.

6.2 Informed Consent Process

The Principal Investigator or his/her authorized designee will conduct the Informed Consent Process, as required by applicable regulations and the center's Institutional Review Board (IRB) / Ethics Committee (EC). 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. 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/EC. 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 by the person obtaining the consent, prior to any clinical trial/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.

The Principal Investigator or his/her authorized designee will document the informed consent process in the subject's hospital and/or research charts. The date of signature will be entered on an applicable Case Report Form (CRF).

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 if enrolled at a US investigational site.

For Live cases at congresses the patients need to sign a specific Live Case ICF, approved by the IRB. The investigator must notify Abbott Vascular prior to performing a Live Case. FDA approval is also required for a live case conducted in US.

Failure to obtain informed consent from a subject prior to any study related procedure or collection of study related data must be reported to Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/ EC'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 will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

No vulnerable populations will be recruited for this clinical investigation. Vulnerable patients are defined as patients whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority, are excluded from the study population. Individuals under the age of 18 or age of legal consent are excluded from the study population. Additionally, pregnant or breastfeeding women 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 and he/she 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.

6.3 Screening

Potential patients presenting at the investigational sites will be fully informed about the clinical investigation, following the established Informed Consent process (described above). Once a dated and signed Informed Consent Form is obtained, the screening procedures may begin.

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

1) Clinical indication for angiography with potential for PCI
2) Inclusion and exclusion criteria

In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screen failure. Records of patients who are screened will be maintained and submitted to the sponsor on a screening log upon request. The Principal Investigator or the delegated study personnel will record the screen failure in the hospital records and on a screening log as required.

6.4 Point of Enrollment

Subjects are considered enrolled in ILUMIEN IV after signing the Informed Consent. Subjects are considered randomized in the trial after the randomization system has been contacted and a study arm (OCT or angiography) has been assigned. Enrolled subjects not randomized or not included as a roll-in subject in the trial will be considered screen failures and will not be followed.

Study participants will be classified as:

Screen Failure
A subject who provides a signed Informed Consent form but fails to meet the eligibility criteria (i.e. does not meet all inclusion or in whom any exclusion criterion is present) and/or does not achieve randomization or is not included as a roll-in subject. Screen Failure subjects will not be part of the analysis cohort and will not be followed but recorded on screening log.

Roll-in Subject
Defined as a non-randomized subject who provides a signed Informed Consent Form, meets all eligibility criteria and undergoes an OCT-guided stent implant procedure using the study methodology. Procedural clinical and safety data will be collected for these patients with follow-up through discharge from the index procedure. Post-discharge assessment of cardiac biomarkers or creatinine are not required for roll-in subjects. Each operator will be allowed up to 3 roll-in subjects. The procedural results, angiograms and OCT technique and data for each roll-in case will be reviewed by the OCT core laboratory director. When it is agreed that the operator has full understanding of the OCT-guidance protocol, the roll-in requirement for that operator will have been completed and randomization may proceed. If after 3 roll-in cases the operator is still not complying with the OCT-guidance protocol, that operator will not be permitted to randomize within the trial. The roll-in phase may be waived for operators who participated in ILUMIEN III in whom expertise with the OCT guidance protocol was already demonstrated. Roll-in subjects will not be included in the analysis group for assessment of the primary imaging and clinical endpoints.

Randomized Subject
Defined as a subject who provides a signed Informed Consent Form and undergoes randomization. These subjects will constitute the primary analysis cohort.

6.5 Scheduled Procedures

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

6.5.1 Baseline

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, sex, ethnicity and race
- 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
- Physical examination: include subject's height, weight (measurements taken during visit)
- Pregnancy test (negative pregnancy test is required for any female of childbearing potential)
- Serum creatinine and hemoglobin measured within 1 week prior to PCI
- Troponin and/or CK-MB within 48 hours prior to PCI. If abnormal must be repeated either 8-16 hours after the last measurement, or drawn from the sheath at the time of the procedure so a curve may be established for peri-procedural MI adjudication. Use of high sensitivity troponin is not recommended.
  Note: patients with stable CAD may have the biomarker drawn from the sheath prior to any intervention, and the result does not need to be available prior to treatment.
- 12-lead ECG
- CHF assessment (by Killip class or NYHA class)
- 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.
- Syntax score for patients with moderately complex 2-vessel disease or any 3-vessel disease. Use the online calculator to determine Syntax score I (http://www.syntaxscore.com). For patients with single vessel disease or simple 2-vessel disease, no calculation is required – record "< 33" for Syntax score.
- Patient Reported Outcome questionnaire (EQ-5D-5L)
- Patients must receive at least 150 mg of oral non-enteric coated aspirin within 12 hours prior to PCI, regardless of prior aspirin use. Intravenous aspirin administration is allowed in geographies where it is standard of care.
- Patients shall receive an appropriate loading dose of an ADP antagonist (clopidogrel, prasugrel or ticagrelor) as per standard of care, preferably within 12 hours prior to, but in all cases no later than 2 hours after PCI. Loading dose of ADP antagonist is not required for subjects receiving chronic treatment of ADP antagonist.

The following considerations apply to subjects having staged procedures, which are described in **Section 6.5.3.8**:

- The protocol required pre-procedure serum creatinine, cardiac enzyme and 12-lead ECG assessments must be repeated for the staged procedure as done for the original index procedure.
- Pre-procedure administration regimen of aspirin and P2Y12 receptor inhibitor (dosage requirements and timing) must be repeated prior to the staged procedure as done for the original index procedure. If the subject has not been discharged between the index and staged procedures, and has received daily aspirin while in hospital, no aspirin reloading is required.

6.5.2 Randomization

Target lesions will be identified based on coronary angiography (plus use of physiological assessment of coronary artery disease as appropriate) for eligibility for PCI. If all inclusion criteria are present and no exclusion criteria are present for at least one target lesion, the patient may be randomized. Randomization should be performed immediately following angiography, or after successful and uncomplicated PCI of one or more lesions in a non-randomized non-target vessel. Randomization is performed before wire crossing or PCI on any lesion in a target vessel is performed with a few exceptions. The lesion may be crossed with a pressure wire to determine its physiological significance and for randomized CTO lesions, for which randomization will occur after successful antegrade wire crossing and successful pre-dilatation with confirmation that the culprit lesion is amenable to OCT-guidance. If the CTO is not successfully crossed with antegrade wire escalation techniques and non successfully pre-dilated, or if complications occur during the CTO recanalization procedure, the patient may not be randomized.

Randomization will be stratified by medication-treated diabetes, presentation with a biomarker positive ACS (NSTEMI or recent STEMI), and site. Randomization allocation will be through an electronic randomization system. A cap of 10% will be implemented for in-stent restenosis in the overall population (see ***Section 5.4.1***, Inclusion Criteria #3.B.vi). Prior to randomization the site will declare to the electronic randomization system the stratification variables. Designation of planned staging may be modified within 24 hours after the procedure if necessary (*see **Section 6.5.3.8** for more details*). The intent to stage will be used by the CEC in determining whether subsequent revascularization procedures are unplanned, thus meeting the criteria for endpoint events. However, even planned staged interventions may be included as an endpoint event if done urgently and sooner than planned for active ischemia.

Note: Each target vessel may contain up to two target lesions, and there may be up to 2 randomized target vessels (i.e. up to 4 target lesions). All lesions in target vessels must be determined by the operator to be amenable to OCT-guided PCI, although only one of the lesions must have high-risk angiographic characteristics.

> Exception: PCI target lesions are not required to meet high-risk angiographic criteria if the patient qualifies for randomization on the basis of medication-treated diabetes.

Note: Planned treatment of more than 2 target lesions per target vessel is not allowed. In cases where treatment of a target lesion reveals unexpected additional lesion(s) in the target vessel, the investigator may treat the unplanned lesions. Unplanned lesions will not be part of the analysis of the primary endpoint of post-PCI MSA but will be included in the analysis of the primary clinical TVF endpoint. Unplanned lesions in the angiography arm should be treated per angiographic standard of care, without intravascular imaging. Unplanned lesion(s) in the OCT arm should be treated per the OCT algorithm if possible.

Additional procedures in target vessel: Subsequent treatment in the target vessel is allowed in circumstances where the operator deems the index procedure to be incomplete and requiring planned continuation in a separate procedure to achieve a successful result. Under these circumstances, the index procedure may be completed on a subsequent day, and the continuation of treatment must be per the original assigned strategy. The subsequent procedure if completed without complication should not be reported as an AE or considered as a revascularization.

6.5.3 PCI Procedure

Following is a description of the image acquisition and treatment steps to be used during the index procedure. All angiographic and OCT data will be stored digitally for subsequent analysis and these images must be sent to the CRF Core Laboratory for analysis.

6.5.3.1 Pre-PCI imaging

At least 100 µg of IC nitroglycerin or appropriate dosage of IC isosorbide dinitrate should be administered prior to diagnostic angiography for both arms of the study, unless precluded by low blood pressure. Anticoagulation for imaging and PCI must be achieved with either unfractionated heparin, bivalirudin or enoxaparin, with or without glycoprotein IIb/IIIa inhibitors, according to local standard of care, prior to insertion of any guidewire for imaging or PCI in a coronary artery.

For subjects in the OCT arm, imaging is recommended to be performed using the motorized pullback device at 75 mm pullback, 5 frames per mm over 2.1 secs for OCT. If possible, the imaging run should start at least 1 cm distal to the angiographic extent of the lesion and continue until the end of image acquisition for OCT. If the imaging catheter will not cross the lesion prior to stenting, vessel preparation (balloon pre-dilatation – standard, cutting or scoring balloon, or atherectomy), with or without a guide extension catheter, may be used to facilitate OCT imaging catheter passage prior to stenting. The necessity for lesion preparation prior to OCT imaging will be collected on the case report form. In all cases, however, OCT imaging should be performed, if at all possible, prior to stent implantation in the OCT arm. In the event the OCT catheter cannot pass despite adequate lesion preparation facilitated with a guide catheter extension, the investigator should perform the intervention as per local standard of care and follow the OCT guided algorithm following stent placement. In the event that the OCT catheter cannot pass even after stent placement, treatment should be per local standard of care.

If available, the OPTIS Integrated system angiographic co-registration function should be utilized. If OCT angiography co-registration is not available, during the OCT pullback, a cine angiogram must be acquired and the OCT pullback then co-registered with the angiogram by visual estimation.

Planned usage of ≥2.5 mm and ≤3.5 mm stents and post-dilatation balloons is required based on pre-PCI angiographic visual estimation. After assessment of pre-dilatation and/or stent implantation result, usage of post-dilatation balloons outside of this diameter range is allowed per investigator judgment. This instruction applies to both OCT-guided and angiography-guided arms.

Note: Intravascular ultrasound must not be used in the target vessel in either the OCT-guided or angiography-guided arm except in bailout only for an emergent, life-threatening condition such as acute closure without obvious cause.

6.5.3.2 Randomization to angiography-guided stenting

If the patient is randomized to angiography-guided stent implantation, stenting will be performed and optimized with angiography guidance according to local standard practice. Quantitative coronary angiography (QCA) is not required. At the end of the stent procedure, at the time the operator would be otherwise removing the guidewire and taking final completion angiography, a blinded OCT must be performed for submission to the core laboratory. This blinded OCT run is for study purposes only – the operator may not view the OCT results, and may not make additional treatment decisions on the basis of this OCT image acquisition. To do so will be considered a major protocol violation.

The operator may obtain feedback from a member of the team, such as a technician, nurse, study coordinator etc. as to whether the final blinded OCT run was technically adequate, with good lumen clearance, capturing at least 10 mm distal and 10 mm proximal to the stented segment. At least 100 µg of IC nitroglycerin or appropriate dosage of IC isosorbide dinitrate should be administered for each target vessel treated prior to the final angiographic and OCT images, unless precluded by low blood pressure. Following the blinded OCT run, a final test coronary contrast injection or recorded cine angiogram may be taken to insure vessel patency without complication. In the event the index procedure in the angiography guided arm becomes prolonged and a second procedure is needed to complete stent implantation, the blinded OCT run may be performed in the second procedure when the operator deems that target vessel treatment is complete. No other intravascular imaging may be performed, and no additional treatment decisions may be made on the basis of the OCT image acquisition.

6.5.3.3 Randomization to OCT-guided stenting

If the patient randomizes to OCT-guided stent implantation, stenting will be performed with OCT-guidance according to a slightly modified version of the ILUMIEN III:OPTIMIZE PCI algorithm,[19] as described below **(Figures 1a-b, 2 – 5)**. The procedure for OCT-guided stent implantation can be found in the flowchart in **Figure 1a**, and details for post-implant stent optimization can be found in the flowchart in **Figure 1b**. OCT is required pre- and post-stent implantation for patients randomized to OCT-guided stent implantation**.** The one exception is that in the case of a 2-stent bifurcation lesion: pre-stent OCT imaging is required in both main and side branches, but post-stent OCT imaging is required in the main branch only. Post-stent OCT imaging in the side branch is recommended but not required. For the evaluation of stent expansion in the side branch of 2-stent bifurcation lesions, MSA in the side branch will be compared to the side branch distal reference (i.e. division of the stented segment in side branch into halves is not required). For any bifurcation, within a lesion, where the side branch is visually estimated to be ≥2.5mm, the branch must be protected with a guide wire during PCI to prevent abrupt closure, irrespective of whether it is planned for provisional or 2-stent strategy.

Following completion of stenting in the target vessel (of one or two target lesions), when the angiographic appearance is considered optimal and all interventional equipment would be otherwise removed, a post-PCI OCT run is performed as depicted in **Figure 6**. If additional PCI is required and performed based on the findings of the post-PCI OCT acquisition (to optimize the result based on the OCT findings per the modified OPTIMIZE PCI algorithm[19]), an additional OCT run must be performed to record the impact of the OCT-guided optimization. Instructions for the management of suboptimal deployment characteristics of underexpansion, major malapposition, dissections and untreated reference segment disease is detailed in **Section 6.5.3.7**. In the event the index procedure in the OCT arm becomes prolonged and a second procedure is needed to complete stent implantation, the post-PCI OCT run may be performed in the second procedure when the operator deems that target vessel treatment is complete.

At least 100 µg of IC nitroglycerin or appropriate dosage of IC isosorbide dinitrate must be administered for each target vessel treated prior to the final angiographic and OCT image acquisition, unless precluded by low blood pressure.

OCT images should be acquired using a 75 mm pullback over 2.1 seconds accruing 5 frames per mm. For standard pullback using power injectors (recommended) such as the ACIST or Medrad device, 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. For large vessels, excessive tortuosity or lesions in the distal 3rd of the culprit vessel, 4 ml/sec for 4 seconds and thus 16 mL of contrast is recommended. For operators using manual injection, the recommended contrast injection volume is 14 ml in

the left coronary artery and 12 ml in the right coronary artery. Performing cine angiography in the desired angiographic view(s) during OCT pullback to maximize utility of delivered contrast is mandatory.

6.5.3.4 Selection of the Stent Diameter by OCT

Stent diameter will be determined by measuring the distal reference EEL to EEL diameter, if visible by OCT (which was the case in 77% of distal reference segments in ILUMIEN III:OPTIMIZE PCI [19]) (**Figure 1a**). The stent diameter must be chosen using the EEL to EEL diameter(s) at the distal reference, rounded down to the next stent size. For example, if the distal reference EEL measures 3.2 mm x 3.1 mm, the mean EEL is 3.15 mm, and thus a 3.0 mm stent diameter should be chosen**.**

Note: In the case where the EEL is equal to an existing stent size, the stent chosen should be equal to the EEL measurement. No rounding down is required.

As described in **Figure 1a**, if the distal reference EEL cannot be identified, the stent diameter should be chosen using the mean lumen diameter at the distal reference, rounded up to the next stent size. For example, if the distal reference lumen measures 2.5 mm x 2.6 mm, the mean lumen diameter is 2.55 mm, and thus a 2.75 mm stent diameter should be chosen**.** If the distal reference EEL can be identified, it must be used instead of mean lumen diameter to choose the stent diameter.

Note: In the case where the lumen diameter is equal to an existing stent size, the stent chosen should still be the next larger stent size. Rounding up is always required.

In cases where the luminal border cannot be adequately visualized by OCT, the reference sites and stent size (length and diameter) will be determined by angiography – such occurrences will be collected in the case report form and should be very infrequent.

If a XIENCE stent of the appropriate diameter is commercially available but not in stock at the study site, a XIENCE stent diameter must be used that will adequately expand with post-dilatation to the intended dimensions; usually this will be the next smallest diameter. If that XIENCE diameter size is also not available, a competitive DES of the appropriate diameter must be used and a protocol deviation must be recorded.

The procedure for post-implant stent optimization per EEL diameter and per lumen diameter is shown in **Figure 1b**. Examples of EEL and lumen based measurements are shown in **Figures 2 and 3**. Note, the EEL need not be contiguous for the purposes of choosing stent diameter. If there is sufficient EEL present on either side of the vessel to allow measurement through the middle of the vessel (**Figure 2C and C'**), the EEL can and should be preferentially used to choose stent diameter.

Planned use of only ≥2.5 mm and ≤3.5 mm stents and post-dilatation balloons based on pre-PCI angiographic visual estimation is required. If after pre-PCI OCT assessment it is determined from the procedure described above that stents and/or balloons larger (or smaller) than this diameter range should be used, this is acceptable and the proper diameter stents and/or post-dilatation balloons must be used per OCT protocol guidance. Note that in long tapering lesions, the use of large balloons should be limited to that portion of the stent where the EEL diameter measurements are at least as large as the stent or balloon diameter.

There must be an intent to stent (planned stent implantation) of all target lesions for trial eligibility. However, if OCT assessment of a target lesion with in-stent restenosis (ISR) shows that the predominant mechanism of the ISR is underexpansion (not neointimal hyperplasia), then balloon only treatment without additional stent is allowed.

6.5.3.5 Assessment of the Target Lesion Length by OCT

The proximal and distal reference segments are initially identified by angiography, and then confirmed by performing pre-procedural OCT pullback across the target segment (**Figure 1a**). In cases in which a severe stenosis would interfere with distal clearance of blood, or if the lumen border at both (proximal and distal) reference segments cannot be detected by OCT, vessel preparation is strongly recommended with balloon dilatation or other modalities (e.g. cutting balloon, atherectomy, thrombectomy, etc.) deemed necessary by the operator, followed by OCT.

When the lumen borders at both reference segments can be measured, the reference sites will be decided by the position with the largest lumen using the OCT Lumen Profile software, where sufficient external elastic lamina is visible to allow measurement of stent diameter, typically several mm away from the angiographic lesion shoulders. If sufficient EEL cannot be visualized at the initially chosen reference cross-section, the reference cross-section is adjusted ±5 mm to identify a cross-section where the EEL is visible sufficient to allow stent diameter measurement. The stent length will be determined by measuring from the distal to the proximal reference site using the OCT Lumen Profile software. A XIENCE stent of appropriate length should be selected to be implanted in these reference segments if possible. See example in **Figure 4.** If a XIENCE stent of the appropriate length is commercially available but not in stock at the study site, a competitive DES of the appropriate length must be used and a protocol deviation must be recorded. Overlapping XIENCE stents must only be used for planned treatment of long lesions where a XIENCE stent of appropriate length is not commercially available.

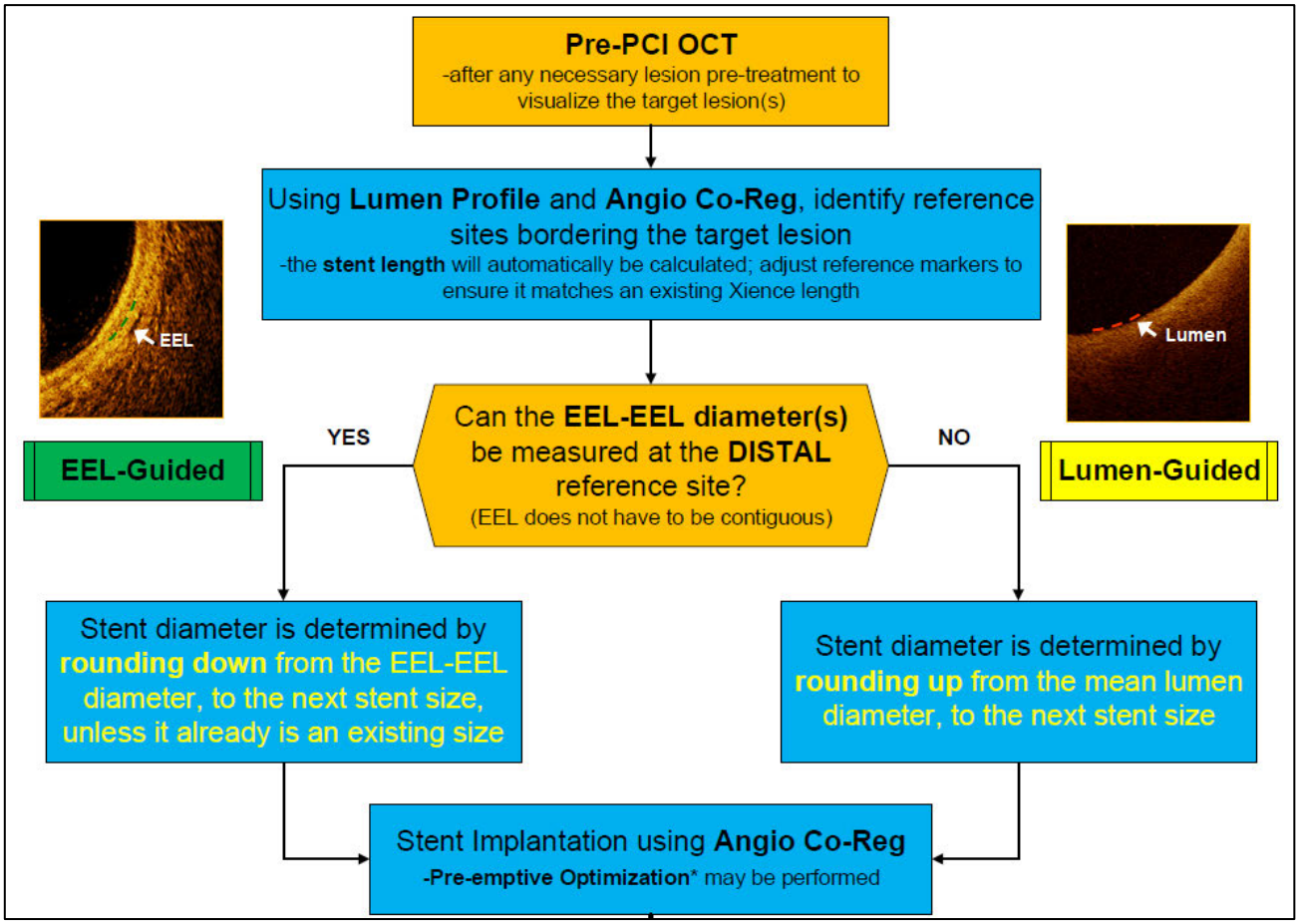


Figure 1a. Procedure for OCT-guided stent implantation. Vessel diameter must be assessed by the EEL-EEL diameter at the reference segment unless the EEL cannot be identified there.

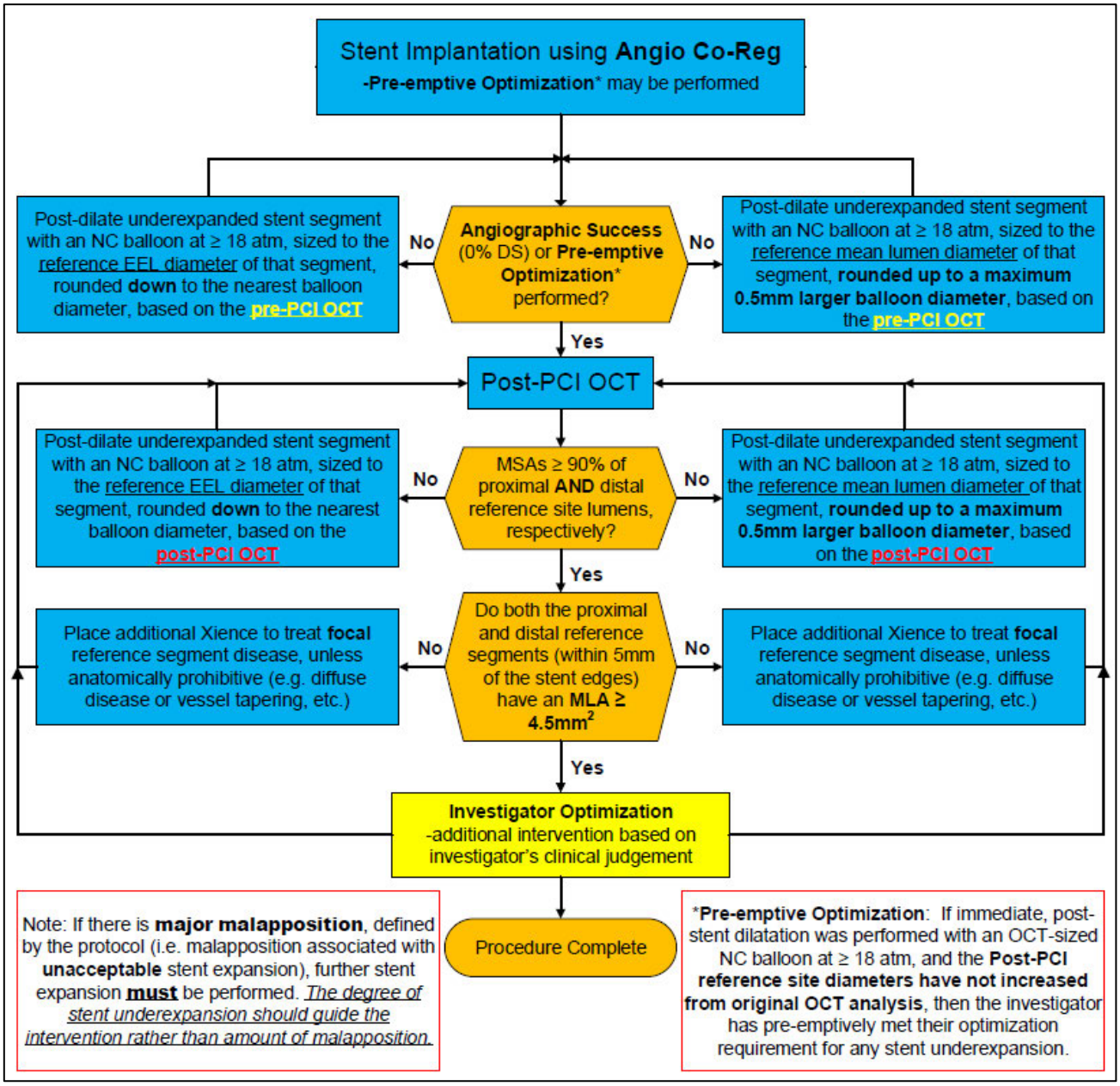


Figure 1b. Procedure for post-implant stent optimization per EEL diameter and per lumen diameter

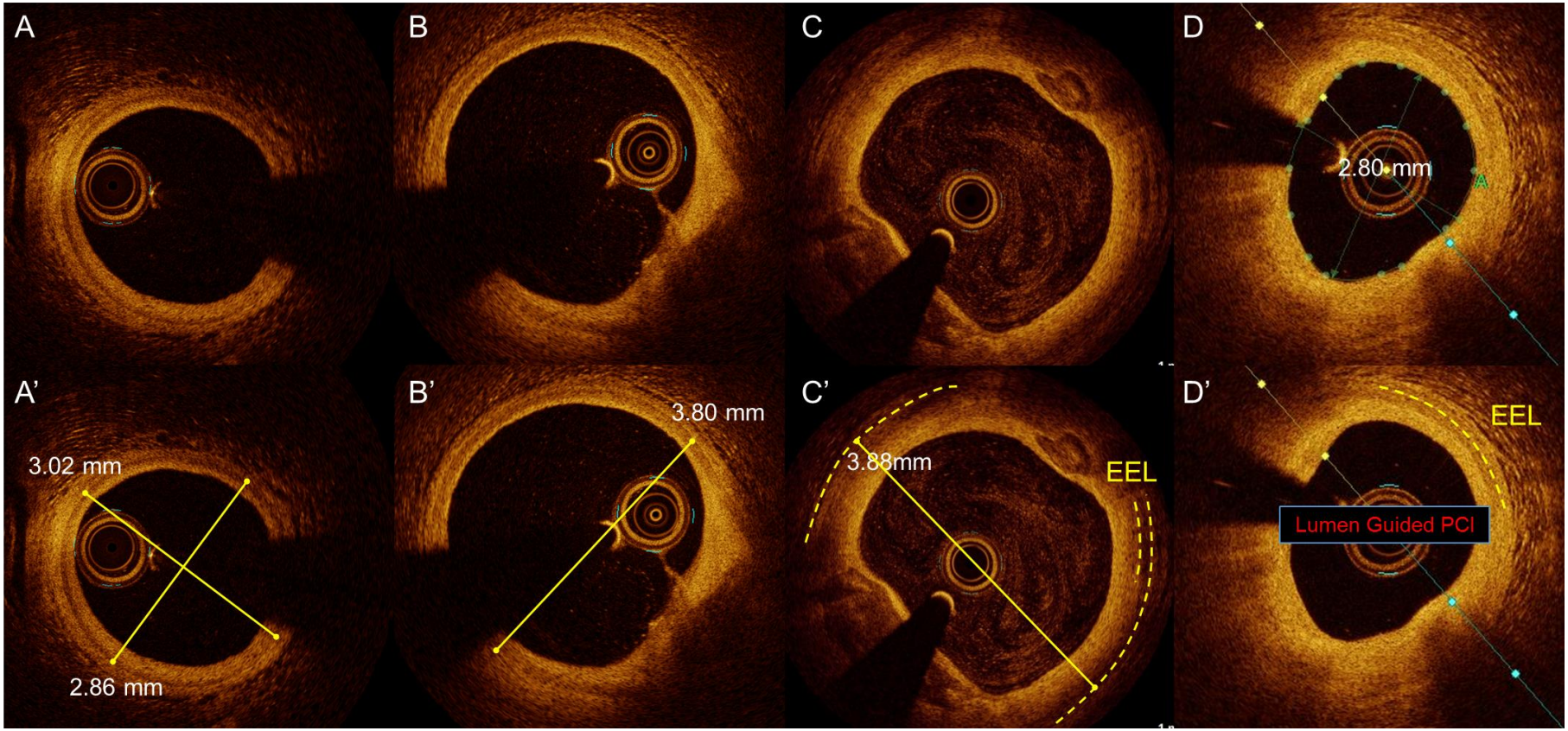


Figure 2. EEL measurement for determination of stent diameter. Stent diameter should be determined by measuring the distal reference mean-EEL diameter, if visible by OCT, rounded down to the nearest available Xience stent diameter. A-A') The distal reference EEL measures 3.02 mm x 2.86 mm; the mean EEL is 2.94 mm, and thus a 2.75 mm diameter Xience stent should be chosen**.** B-B') If only a single EEL measurement is possible, this measurement should be used for determination of stent diameter. In this case the distal reference EEL measures 3.80 mm. Thus a 3.50 mm diameter Xience stent should be chosen**.** C-C') The distal reference EEL measures 3.88 mm. Note, a single EEL measurement is possible despite non-contiguous EEL measures. This measurement should be used for determination of stent diameter. Thus a 3.50 mm diameter Xience stent should be chosen**.** D-D') The distal reference EEL can only be measured on a single side of the vessel, precluding the use of the EEL for measurement of stent diameter. The mean lumen diameter, upsized to the closest stent size, should be used to determine stent diameter. In this case the lumen diameter was 2.98 mm x 2.61 mm; the mean lumen reference diameter was 2.80 mm, and thus a 3.00 mm Xience stent should be chosen.

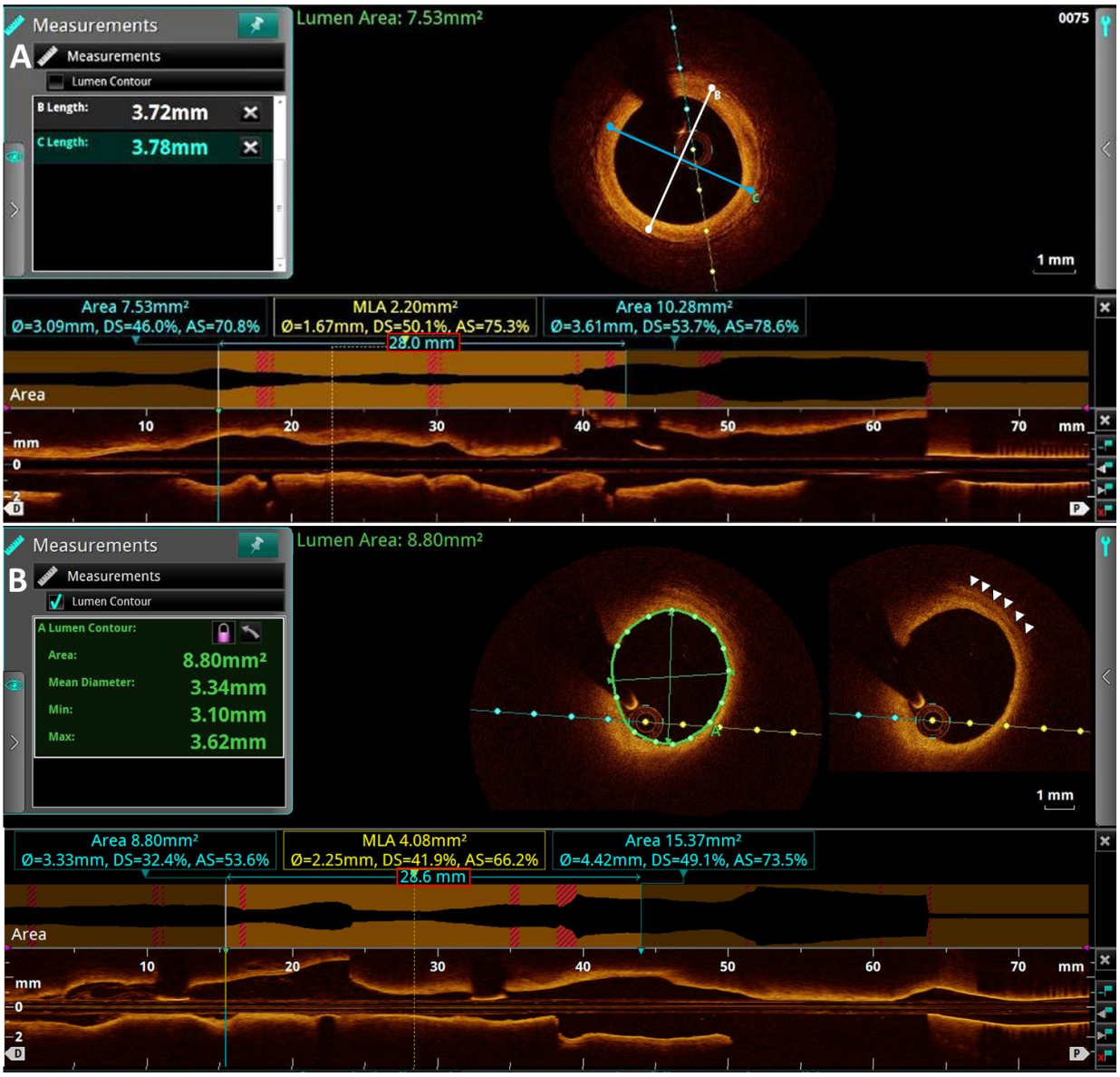


Figure 3. OCT-guided stent sizing.

When the vessel diameter can be determined by EEL reference segment measurements, the mean EEL to EEL diameter should be used to determine stent diameter. **Example A**) Two measurements of vessel diameter from EEL to EEL are shown using the measurement function. 3.72 mm (white text) and 3.78 mm (blue text) corresponding to the white and blue measurement lines on the OCT cross-section. Per protocol the mean of these two measurements ((3.72+3.78)/2 = 3.75 mm) is rounded down to the nearest stent size, and therefore a 3.5 mm diameter stent is chosen. The distance from distal to proximal reference (red box) is 28 mm, and thus a 3.5 x 28 mm Xience stent is chosen.

When the vessel diameter cannot be determined by measurement to the EEL, the mean lumen diameter should be used to determine stent diameter. **Example B**) The EEL is only visible in a single quadrant of the OCT cross-section (white arrows). Automated measures identify the mean reference lumen diameter as 3.34

mm. Per protocol the mean lumen diameter is rounded up to the nearest stent size, and therefore a 3.5 mm diameter stent is chosen. The distance from distal to proximal reference (red box) is 28.6 mm, and thus a 3.5 x 28mm Xience stent is chosen.

6.5.3.6 Stent Implantation and Initial Optimization

Stent implantation should be guided by angiographic co-registration, if available. Positioning stents at the intended segments can be confirmed with angiographic co-registration to improve the accuracy of stent placement and reduce geographic miss (**Figure 5**).

After initial stent deployment and angiographic optimization procedures (including post-dilatation and/or additional stents as necessary), if the visually assessed residual angiographic diameter stenosis is >0%, OCT-guided PCI optimization *based on the pre-PCI OCT run* should be performed to achieve this angiographic target. Post dilatation should be performed in the angiographic segment with visually assessed diameter stenosis >0% using non-compliant balloons at ≥18 atmospheres with diameter no larger than the closest pre-PCI OCT mean reference vessel EEL (if the EEL is visible) (**Figures 1b and 3**), or if the EEL was not measurable, up to 0.5 mm larger than the closest pre-PCI OCT mean reference lumen diameter (**Figures 1b and 3**).

Important: Caution should be exercised in the post-dilatation of long stented segments (≥28mm) in cases where the stent is located in a tapering vessel and/or where the stent covers multiple side branches. Caution should also be exercised in the post-dilatation of lesions with severe calcification (especially calcific protruding nodule) or vessel angulation. If there is underexpansion in one or more locations within the stented segment, post-dilatation should be limited to the underexpanded location(s) using a short focal balloon(s) (6 – 8 mm in length) having diameter that is appropriately matched to vessel size at that location.

6.5.3.7 Post-Stent Implantation OCT

If after initial stent deployment, (including post-dilatation and/or additional stents as necessary), the visually assessed residual angiographic diameter stenosis is ≤0%, or pre-PCI OCT guided optimization has already been performed (as described in section 6.5.3.6) OCT should be performed to determine whether acceptable stent expansion is present (defined as MSA of the proximal segment ≥90% of the proximal reference lumen area and MSA of the distal segment ≥90% of the distal reference lumen area) **(Figures 1b, 4-6).** If the OCT catheter will not cross the lesion after stenting, additional post-dilatation is recommended to facilitate catheter passage. If *based on the post-PCI OCT* run acceptable stent expansion is not present, regardless of whether or not accompanied by major malapposition, post dilatation must be performed in the segment(s) with underexpansion using non-compliant balloons at ≥18 atmospheres with the balloon diameter no larger than the closest *post-PCI OCT* reference vessel EEL to EEL diameter (if the EEL is visible) **(Figure 1b),** or up to 0.5 mm larger than the closest *post-PCI OCT* mean reference lumen diameter (if the EEL is not measurable) (**Figure 1b**). In the event of balloon-only treatment of ISR lesions (where stent underexpansion is the primary mechanism for ISR), acceptable stent expansion may be defined as minimal lumen area (MLA) of the proximal segment ≥90% of the proximal reference lumen area and MLA of the distal segment ≥90% of the distal reference lumen area.

After post-dilatation, OCT should be repeated to determine whether acceptable stent expansion has been achieved **(Figure 4-6).** If underexpansion is revealed in the proximal and/or distal segments, at least one round of further stent optimization with higher inflation pressures and/or larger balloons is required. However,

the diameter of the non-compliant post dilatation balloon chosen should not be larger than the post-PCI OCT determined mean reference vessel diameter (EEL) (**Figure 1b**), or no more than 0.5 mm larger than the mean reference segment lumen nearest to the dilatation site (if the EEL cannot be measured) (**Figure 1b**). In situations where the reference EEL is very large (≥ 4.5 mm), the operator is asked to consider using the OCT automated mean reference segment lumen rounded up no more than 0.5 mm to select post-dilation balloon. While it is recommended that further PCI attempts be made until the protocol-defined optimal stent expansion is achieved, it is up to the operator to decide the number and degree of further interventions, at all times taking into account patient safety.

If major malapposition (i.e. malapposition associated with unacceptable stent expansion) is detected by operator assessment during the procedure in the OCT-guided arm, further stent expansion must be performed. The degree of stent underexpansion (acceptable or unacceptable) should guide the intervention rather than amount of malapposition.

If a long stent (≥28mm), was required to cover the lesion such that the proximal and distal reference lumen dimensions were different by ≥ 0.5 mm, then multiple non-compliant balloons of different diameters should be chosen for proximal and distal inflation to achieve optimal stent expansion in each stent segment with underexpansion. If the underexpansion is located in the midsegment of a long stent (≥28mm), post-dilatation within the middle segment should be performed with a balloon sized to the average of the proximal and distal reference measurements.

For PCI optimization, whenever EEL-EEL measurement is possible, this measurement should be used rather than luminal measurements to optimize the respective segment (proximal or distal) of the stent with underexpansion. For example, if two opposing segments of EEL can be measured to choose stent diameter at the distal reference but not the proximal reference, and both are under-expanded post PCI, the distal segment of the stent should be treated using EEL-guided optimization (**Figure 1b**) and the proximal segment of the stent should be treated using lumen-guided optimization (**Figure 1b**).

Following OCT-guided stent expansion optimization, the proximal and distal reference segments, defined as 5mm from the edges of the stent, are examined for inflow/outflow disease (**Figure 6**). If both the proximal and distal reference segments have an MLA ≥4.5 mm^2, no further treatment is necessary. If there is untreated reference segment disease defined as focal MLA< 4.5 mm^2 in either proximal or distal reference segments following the additional OCT run, an additional DES must be placed unless anatomically prohibitive (e.g. biological vessel tapering, distal diffuse disease, absence of landing zone, etc.). If there is a major edge dissection, defined as ≥60 degrees of the circumference of the vessel at site of dissection and ≥3 mm in length, it is recommended that additional DES be placed to correct the abnormality unless anatomically prohibitive (e.g. biological vessel tapering, distal diffuse disease, absence of landing zone, etc.).

Following OCT-guided stent edge and reference segment optimization, the procedure should be complete and a final OCT run must be performed. If any other additional PCI is performed on the study lesion after OCT-guided stent edge and reference segment optimization, a final OCT run must be performed.

If after OCT optimization, additional intervention is deemed necessary by the investigator, they are free to do so. but an additional OCT pullback with associated algorithmic assessment must always follow each round of optimization.

No further intervention may be performed following the final OCT, although coronary contrast injection or recorded cine angiogram may be taken to insure vessel patency without complication after wire and catheter removal.

An example of the OCT guided protocol is shown in **Figures 4-6**.

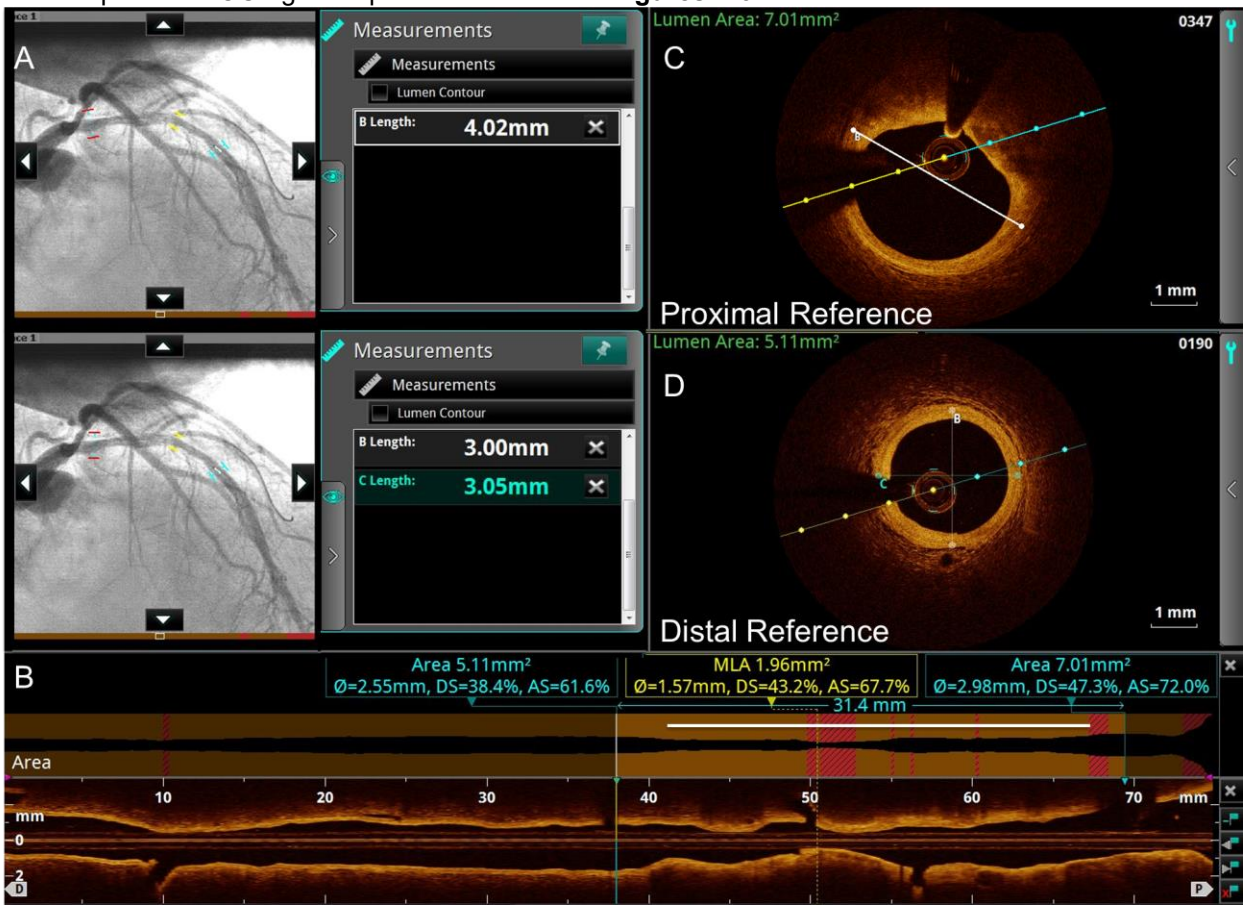


Figure 4. Pre-PCI OCT with proximal and distal reference images.
A) OCT at baseline confirmed that the locations of the distal (blue) and proximal (red) reference segments as suggested by angiography were appropriate, being minimally diseased. **B)** The lesion length was determined by OCT to be 28 mm (white bar). OCT cross-sectional images were scrolled from the edges of the lesion on either side to identify vessel segments with minimal disease and clearly identifiable EEL, resulting in the choice of a 34 mm long stent. **C)** At the proximal reference segment approximately 180 degrees of EEL is visualized, allowing a single measurement of EEL for stent sizing through the middle of the vessel. The measured EEL diameter of the proximal segment (B, white line) was 4.02mm. A mean EEL diameter could not be calculated as only one EEL measurement could be made. **D)** At the distal reference segment 360 degrees of EEL are visualized, allowing multiple measurements of EEL for stent sizing. The measured EEL diameters of the distal reference segment were (B, white line) 3.00 mm and (C, blue line) 3.05 mm resulting in a mean EEL diameter of 3.03mm. The smallest mean EEL diameter from both distal and proximal reference segments was 3.03mm (distal reference) and per protocol this was rounded down to the nearest 0.25mm and thus a 3.0 mm diameter by 34 mm long stent was chosen.

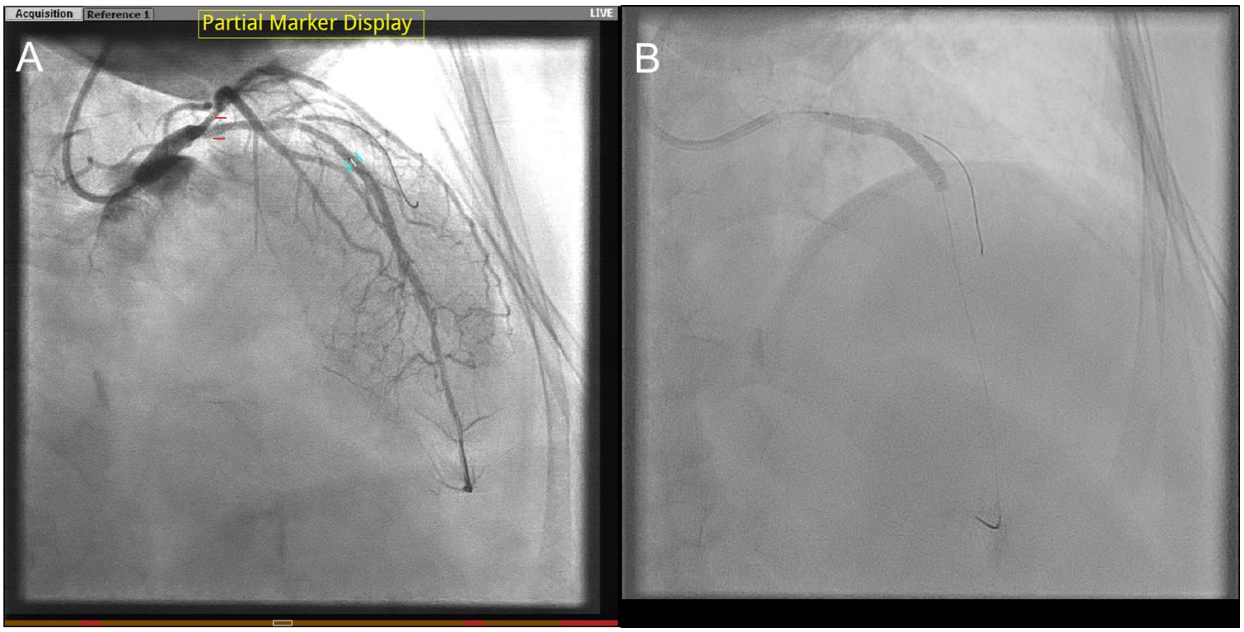
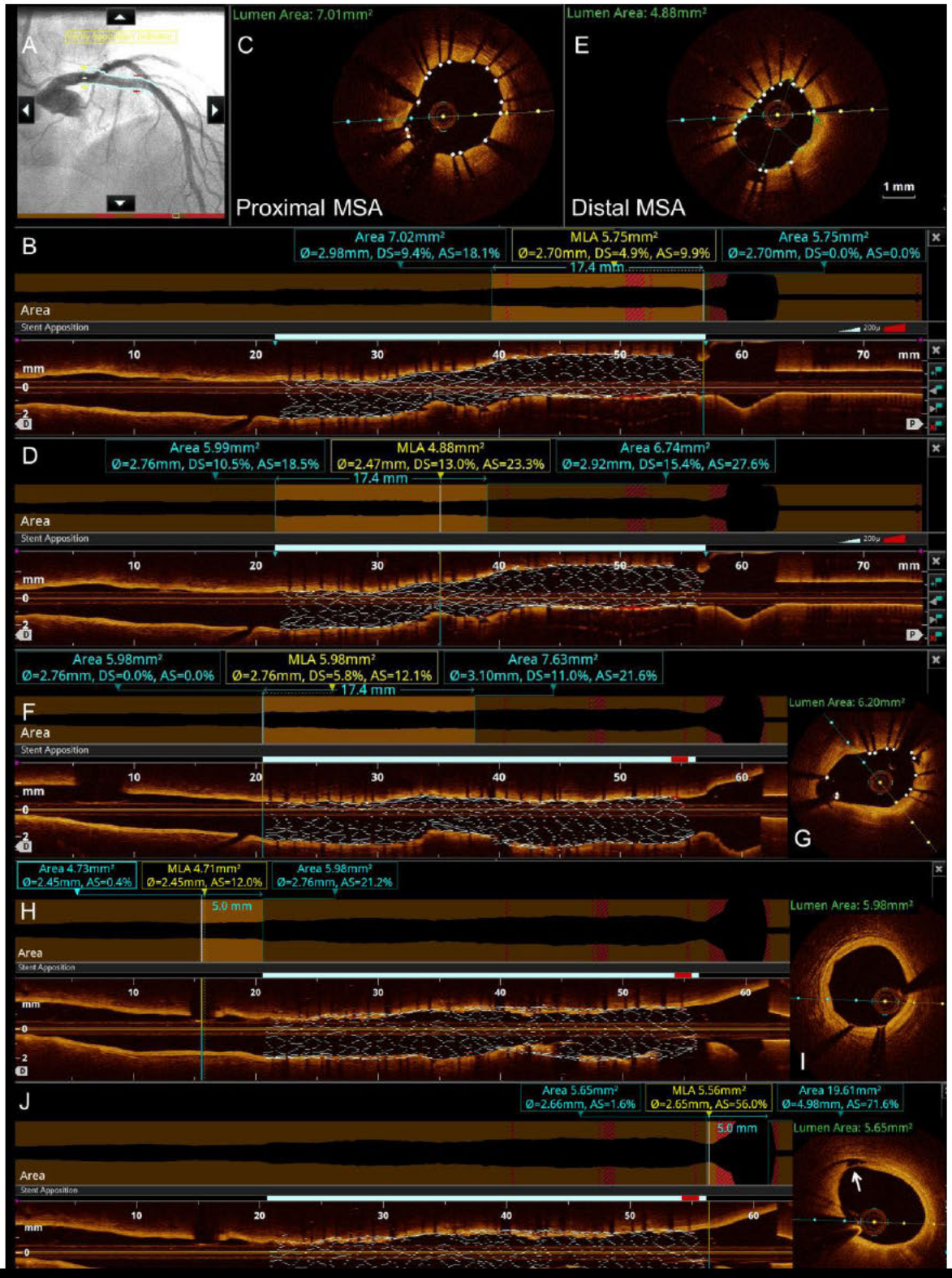


Figure 5. Angiographic co-registration guided stent implantation.
A) OPTIS OCT angiographic co-registration is activated, allowing visualization of the proximal reference (red marker in Figure 5A, and panel C in Figure 4) and distal reference (blue marker in Figure 5A and panel D in Figure 4), and used as a reference screen to guide stent placement.
B) Stent implantation location on real time fluoroscopy is based upon the OPTIS OCT angiographic co-registration reference screen.


A
Lumen Area: 7.01mm²
C
Proximal MSA
Lumen Area: 4.88mm²
E
Distal MSA
1 mm
B
Area 7.02mm²
Ø=2.98mm, DS=9.4%, AS=18.1%
MLA 5.75mm²
Ø=2.70mm, DS=4.9%, AS=9.9%
Area 5.75mm²
Ø=2.70mm, DS=0.0%, AS=0.0%
17.4 mm
Area
Stent Apposition
D
Area 5.99mm²
Ø=2.76mm, DS=10.5%, AS=18.5%
MLA 4.88mm²
Ø=2.47mm, DS=13.0%, AS=23.3%
Area 6.74mm²
Ø=2.92mm, DS=15.4%, AS=27.6%
17.4 mm
Area
Stent Apposition
Area 5.98mm²
Ø=2.76mm, DS=0.0%, AS=0.0%
MLA 5.98mm²
Ø=2.76mm, DS=5.8%, AS=12.1%
Area 7.63mm²
Ø=3.10mm, DS=11.0%, AS=21.6%
17.4 mm
F
Area
Stent Apposition
Lumen Area: 6.20mm²
G
Area 4.73mm²
Ø=2.45mm, AS=0.4%
MLA 4.71mm²
Ø=2.45mm, AS=12.0%
Area 5.98mm²
Ø=2.76mm, AS=21.2%
H
5.0 mm
Area
Stent Apposition
Lumen Area: 5.98mm²
I
J
Area 5.65mm²
Ø=2.66mm, AS=1.6%
MLA 5.56mm²
Ø=2.65mm, AS=56.0%
Area 19.61mm²
Ø=4.98mm, AS=71.6%
5.0 mm
Area
Stent Apposition
Lumen Area: 5.65mm²
mm
10
20
30
40
50
60
70

[redacted]

Figure 6 (previous page). Post PCI OCT with assessment of stent expansion.
Following baseline OCT for stent selection, pre-dilatation with a 2.5 mm diameter x 15 mm compliant balloon at 12-14 atm was performed. Following this a 3.0mm diameter x 34 mm drug-eluting stent was implanted at 12 atm. **A**) Angiography revealed 0% residual diameter stenosis and per protocol OCT was repeated. Per protocol the stent length was divided in half and criteria for MSA assessed in each half. **B**) In the proximal half of the stented segment, **C)** automated measures measured an MSA of 7.01mm^2 and a proximal reference lumen area of 5.75mm^2 (blue and yellow box) equating to a residual AS of 0.0% ([[1-(7.01/5.75)] x100] = -21.9% area stenosis) confirming criteria for optimal MSA were met. **D)** In the distal half of the stented segment, **E)** automated measures measured an MSA of 4.88mm^2 (yellow box) and a distal reference lumen area of 5.99mm^2 (blue box) and thus stent expansion was unacceptable ([1-(4.88/5.99)] x100] = 18.5% area stenosis). Post-dilation was performed with a 3.0mm diameter x 15mm long non-compliant balloon focused to the area of underexpansion at > 20 atmospheres. **F)** Following post-dilation in the distal half of the stented segment, **G)** automated measures measured an MSA of 6.20mm^2 and a distal reference lumen area of 5.98mm^2 (blue and yellow box) and thus stent expansion was optimal ([1-(6.20/5.98)] x100] = -3.6% area stenosis). OCT imaging post-stent demonstrated no major dissection, malapposition or tissue/thrombus prolapse.

When there is a bifurcation (visually estimated side branch ≥2.5mm) within the lesion, rather than divide the stented segments into halves, the stent is divided at the midpoint of the bifurcation into proximal and distal segments. This facilitates measurement favoring native vessel biology and promotes the use of the proximal optimization technique (**Figure 7**). In situations where there is more than one ≥2.5 mm side branch bifurcation, the division into proximal and distal segment will be at the proximal most side branch.

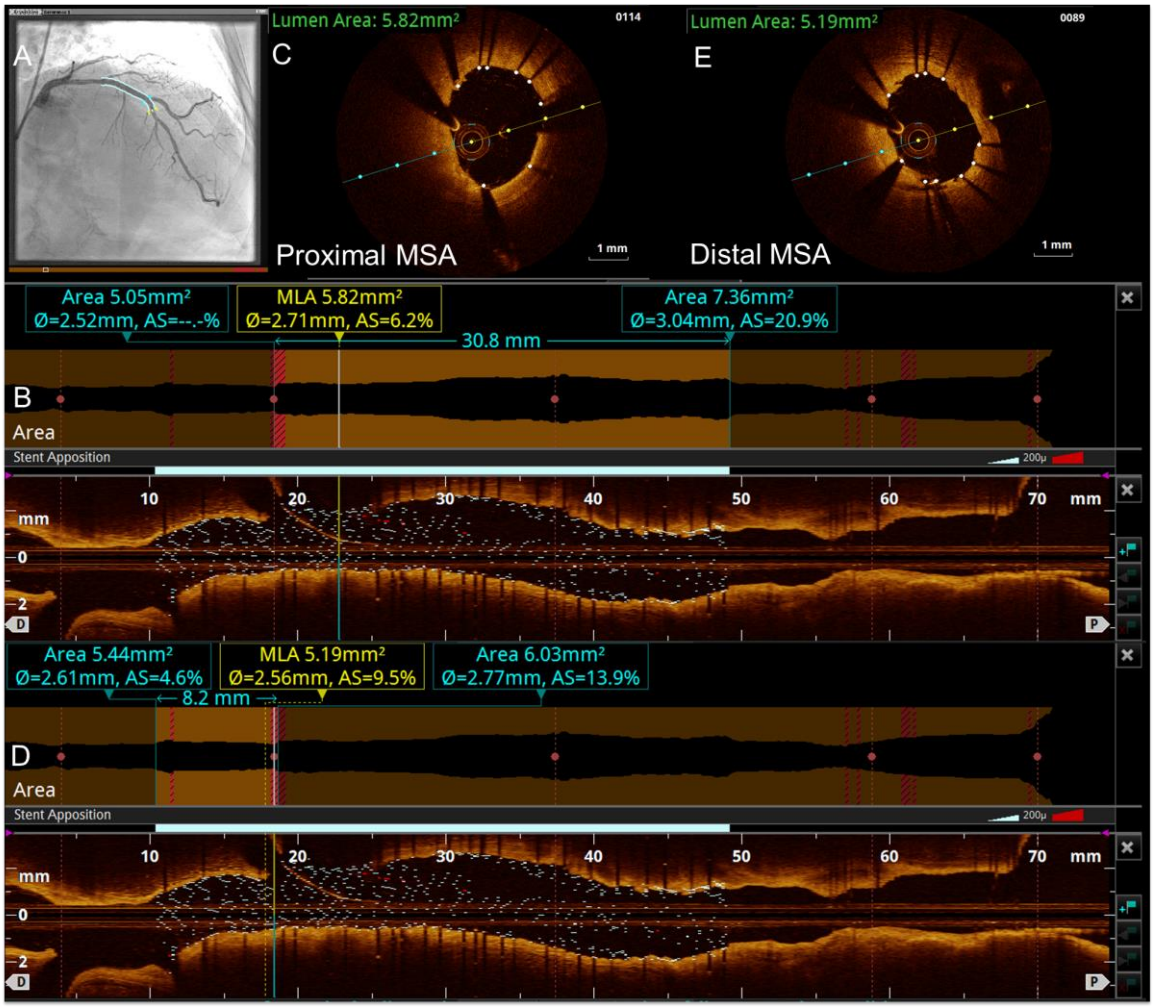


Figure 7. Post-PCI OCT in a long lesion with a non-target lesion bifurcation (provisional)
A) Angiography revealed 0% residual diameter stenosis, and thus per protocol OCT was repeated. **B and C)** Per protocol the stented segment was divided at the bifurcation, facilitated by 3-D bifurcation mode highlighting bifurcations ≥1.5mm (red dot in automated measures), and criteria for MSA assessed in each segment. In the proximal segment, automated measures found an MSA of 5.82 mm^2 (green text) and a proximal reference lumen area of 7.36 mm^2 (blue text) equating to a residual area stenosis (AS) of 20.9% ([[1-(5.82/7.36)] x100] = 20.9%), confirming criteria for MSA were not met and that post-dilation and proximal optimization technique need be performed. **D and E)** In the distal stented segment, automated measures found an MSA of 5.19 mm^2 (yellow text) and a distal reference lumen area of 5.44 mm^2 (blue text), and thus stent expansion was acceptable ([1-(5.19/5.44)] x100] = 4.6% area stenosis, or 95.4% stent expansion).

In situations where there are multiple branches (≥1.5 mm – marked in the bifurcation automated measures feature of the OCT software) within close succession (e.g. septal-diagonal-septal), the operator must take care to not overlap the proximal optimization balloon across multiple branches. Rather, short focal balloons (6-8mm) should be used, ensuring that the proximal optimization balloon does not cross the largest branch. If

the distance to the carina from the proximal reference is shorter than the available length proximal post-dilation balloon, the reference segment should be shifted to just distal to the 1st side branch, similar to the strategy used for stents that land across side branches. For optimization within long segments where there are multiple branches, the diameter of the short focal balloon(s) should be selected to match the reference vessel size within that segment. The appropriate reference segment therefore must be contained within the segment bounded by side branches. Recognition of this fact may thus require post-dilatation with several short non-compliant balloons of different diameters to accommodate the presence of multiple side branches. If following stent implantation in this scenario, there is insufficient length proximal to the first major side branch to perform proximal optimization technique, the reference diameter should be measured just distal to the 1st major side branch and this diameter used for post dilation balloon selection (**Figure 8**).

Large diameter balloons ≥4.5 mm need not be used for post-dilatation if the operator is concerned about the possibility of severe vessel dissection or perforation, even if acceptable expansion has not been achieved with balloon of appropriate diameter and inflation pressure.

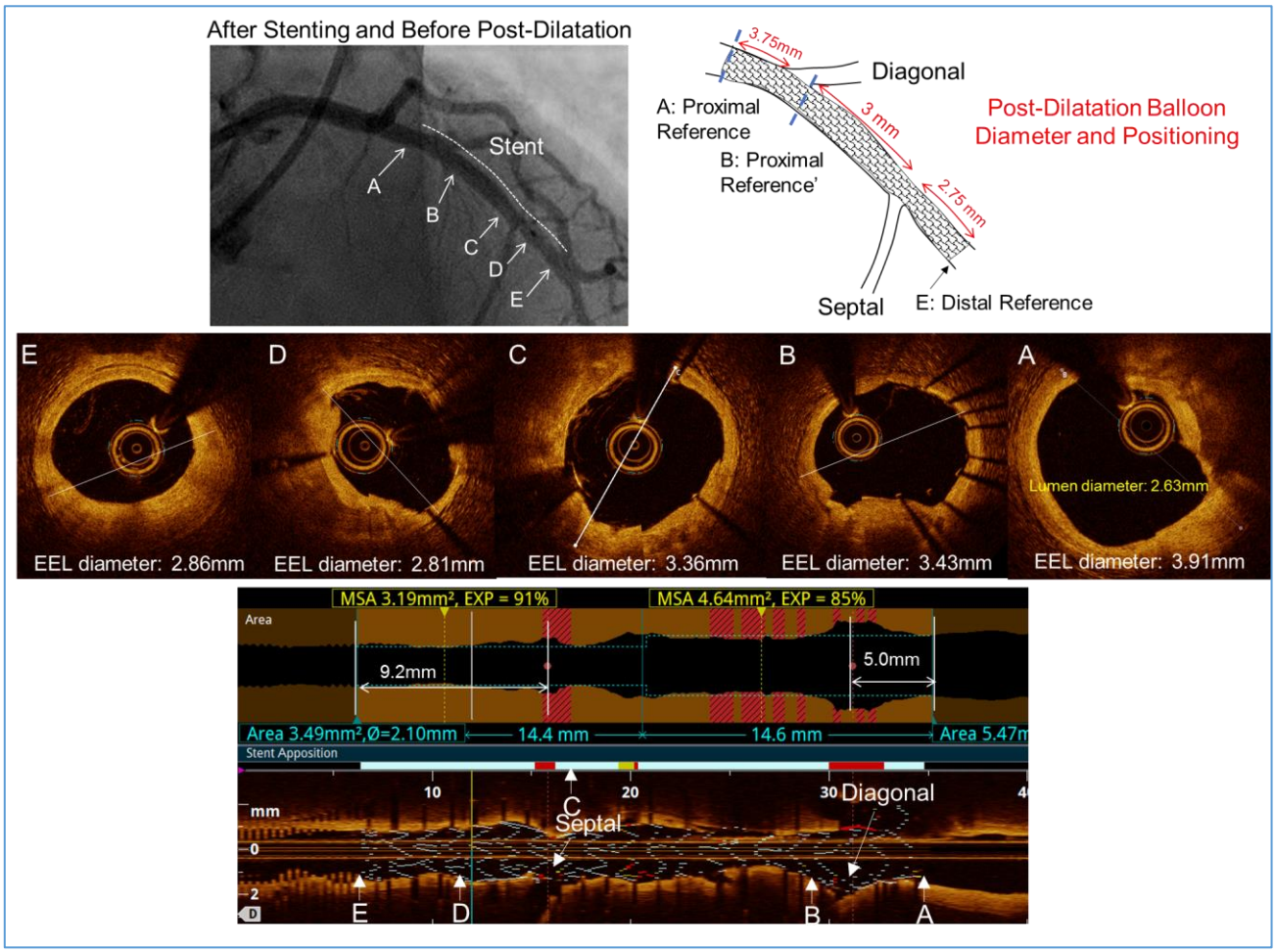


Figure 8. OCT-guided PCI in the presence of multiple side branches.
Following stent implantation, there is proximal underexpansion in this example. Per protocol, the proximal segment of the stent should be post-dilated with a balloon sized to the proximal reference EEL, if visible, and

downsized to the nearest balloon diameter or the mean lumen diameter, upsized up to 0.5 mm if the EEL is not visible. However, in this example the length from the proximal reference (A) to the diagonal branch (B) is shorter than any commercially available balloon. Thus, if the proximal reference (A) EEL measurement (3.91 mm) rounded down to the nearest balloon diameter (3.75 mm) were used even with the shortest available balloon length (6 mm) it would overlap and cross the bifurcation and be oversized. Instead, the correct approach in this example is to shift the proximal reference to (B) proximal reference' (see diagram), just distal to the 1st major side branch. At that location the EEL measurement is 3.43 mm, and per protocol rounded down, would lead to a 3.25 mm non-compliant balloon for proximal post-dilation.

6.5.3.8 *Multivessel PCI*

Patients requiring single or multi-vessel PCI may be enrolled in this trial, including either double or triple vessel disease. Up to 2 target vessels may be randomized. Refer to treatment rules below for cases with a second randomized target vessel. Up to 2 non-target vessels may also be treated, but only one non-target vessel may be treated during the index procedure. In the case of triple vessel disease, at least one non-target vessel must be treated outside the index procedure. Refer to treatment rules below for non-target vessels.

No more than 2 vessels may be treated during the index procedure. The possible combinations of treated vessels during the index procedure are as follows:

1. One vessel disease treatment: 1 target vessel randomized (with 1 or 2 target lesions, all of which must amenable to undergo OCT-guided stenting)
2. Two vessel disease treatment:
    i) 2 target vessels randomized (each with 1 or 2 target lesions, all of which must amenable for undergo OCT-guided stenting)
    ii) 1 non-randomized non-target vessel treated (with no restriction on the number or type of lesions, but all must be treated successfully and without complication), followed by 1 target vessel randomized (with 1 or 2 target lesions, all of which must be amenable to undergo OCT-guided stenting)

Non-target vessels: Non-randomized lesions requiring PCI in up to 2 non-target vessels may be treated either:
a) >30 days prior to the study procedure (in 1 or 2 non-target vessels) if the procedure was unsuccessful or complicated; or
b) >24 hours prior to the study procedure (in 1 or 2 non-target vessels) if the procedure was *successful and uncomplicated* (defined as a final lesion angiographic diameter stenosis <30% for all treated non-target lesions, with TIMI III flow in these vessels, without perforation, cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation, and with no post-procedure biomarker elevation >normal; or
c) during the study procedure (only 1 non-target vessel allowed), in which case all non-target vessel lesions must be treated prior to randomization and such treatment must have been *successful and uncomplicated* (defined more stringently as angiographic diameter stenosis <10% for all treated non-target lesions, with TIMI III flow in this vessel, without final dissection ≥ NHLBI type B, perforation anytime during the procedure, prolonged chest pain (>5 minutes) or prolonged ST-segment elevation or depression (>5 minutes), or cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation); or

d) >48 hours after the index study procedure (in 1 or 2 non-target vessels).

There is no restriction on the number and type of non-target lesions that can be treated in a non-target vessel. PCI in non-target vessels may or may not be guided by OCT (or other intravascular imaging) according to operator preference. XIENCE use is optional to treat non-target vessels; operators may use XIENCE or other DES at their discretion.

A second randomized target vessel: Lesions requiring PCI in a 2nd target vessel (randomized lesions) may be treated during the index procedure (as long as no non-target vessels were treated during the same procedure) or staged >24 hours after the index procedure. However, all staged randomized procedures must be completed within 2 months (preferably 1 month) after the study procedure. The intent to stage such lesions should be declared at the time of randomization, but the decision to stage a randomized vessel which was not originally planned for staging may be modified in the case report form within 24 hours of the procedure to reflect changes in procedural strategy that may arise from the index PCI (e.g. treatment of the first vessel took longer than expected, or was complicated). The original treatment assignment must be used to guide all staged procedures. All staged procedures must be performed in a second target vessel – i.e. staged procedures cannot occur in a second lesion in the first target vessel treated during the index procedure. In no case, however, may a target vessel be randomized which was not declared as intended for study randomization prior to randomization. Note that for staged procedures, the assessments of troponin and/or CK-MB and a 12-lead ECG must be repeated within 8-16 hours prior to the staged procedure. If troponin and/or CK-MB readings are abnormal, they must be assessed either 8-16 hours after the last measurement or drawn from the sheath at the time of the procedure so a curve may be established for peri-procedural MI adjudication. Note: patients with stable CAD may have the biomarker drawn from the sheath prior to any intervention, and the result does not need to be available prior to treatment.

> Example: A stable CAD patient has a significant mid-RCA lesion and a mid-LAD-D1 bifurcation lesion (the latter representing a qualifying target lesion). If the mid-RCA lesion is a non-target lesion (i.e. not declared as a target lesion at the time of randomization), it may be treated a) >30 days prior to the procedure in all cases, or b) >24 hours prior to the procedure if its treatment was successful and uncomplicated; or c) during the procedure but prior to randomization and treatment of the LAD target vessel (if treatment of the RCA lesion is angiographically successful and uncomplicated – if not, randomization of the LAD lesion MAY NOT take place during the same procedure [but may still occur >30 days later if desired); or d) >48 hours after treatment of the randomized LAD lesion. If the mid-RCA lesion is also declared as a target lesion in a second target vessel at the time of randomization (meeting criteria either because it has qualifying angiographic high-risk characteristics, or if the patient has diabetes), it may be treated after randomization either a) during the index procedure in which the LAD is treated (either before or after LAD treatment), or b) >24 hours after the procedure, in which case its treatment as a planned staged procedure is noted in the case report form either before or within 24 hours after LAD treatment.

If a patient has 2 vessels that require treatment during the index procedure and both meet eligibility criteria and qualify as target vessels, at investigator discretion it is permitted to designate one vessel as non-target and the other vessel as target. However, it is encouraged to randomize all qualifying target vessels unless investigator judgment dictates otherwise.

If a patient has 3 vessels where all meet eligibility criteria and would qualify as target vessels – since no more than 2 target vessels may be randomized, it is permitted to designate one of the 3 eligible vessels as non-target. However, it is encouraged to randomize 2 qualifying target vessels unless investigator judgment dictates otherwise.

Multivessel disease treatment flow diagrams depicting the permitted combinations of target and non-target lesions are summarized below in **Figures 9-10** for 2-vessel disease and **Figures 11-12** for 3-vessel disease.

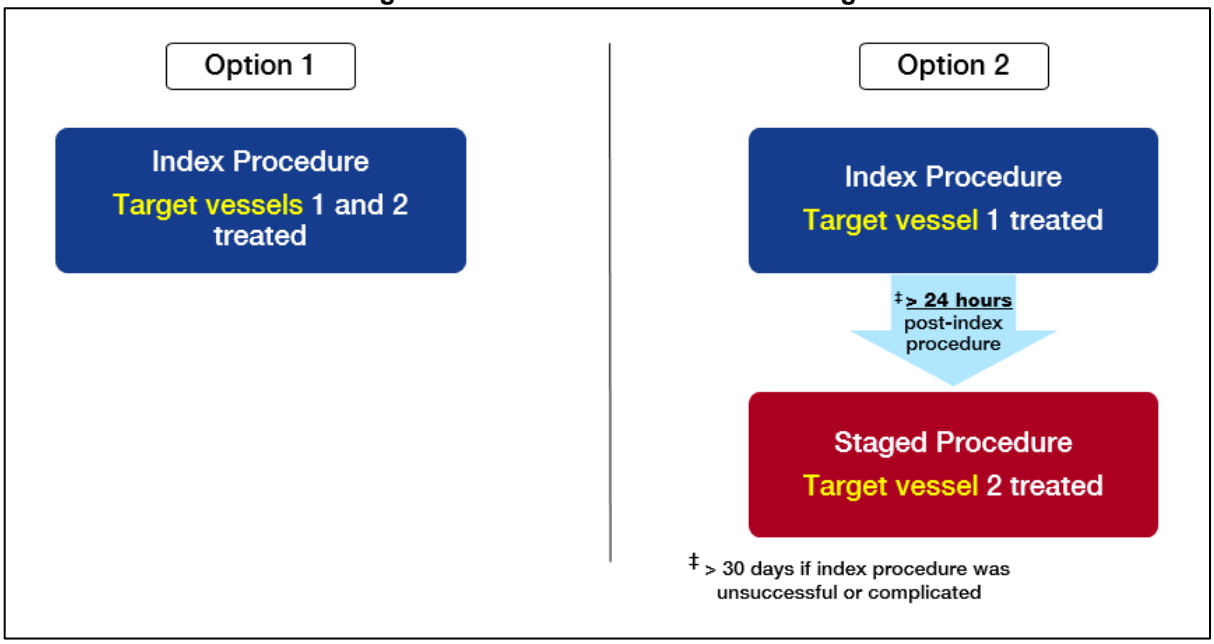


Figure 9. 2-Vessel Disease Treatment: 2 Target Vessels.

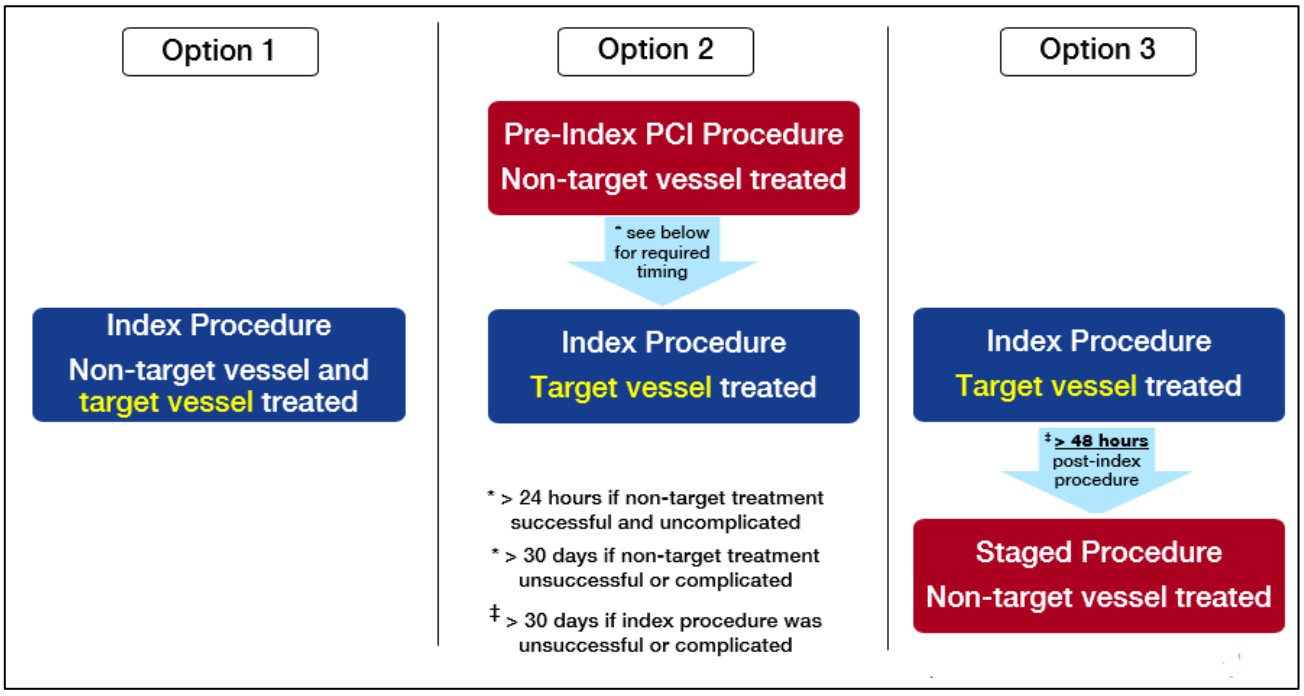


Figure 10. 2-Vessel Disease Treatment: 1 Target Vessel / 1 Non-Target Vessel.

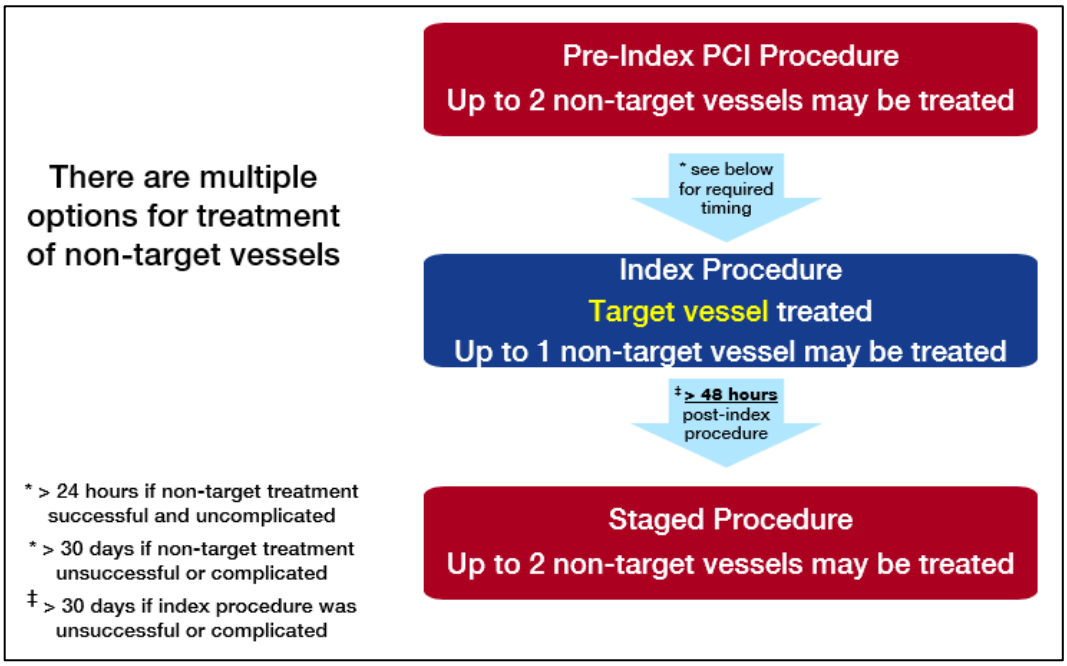


Figure 11. 3-Vessel Disease Treatment: 1 Target Vessel / 2 Non-Target Vessels.

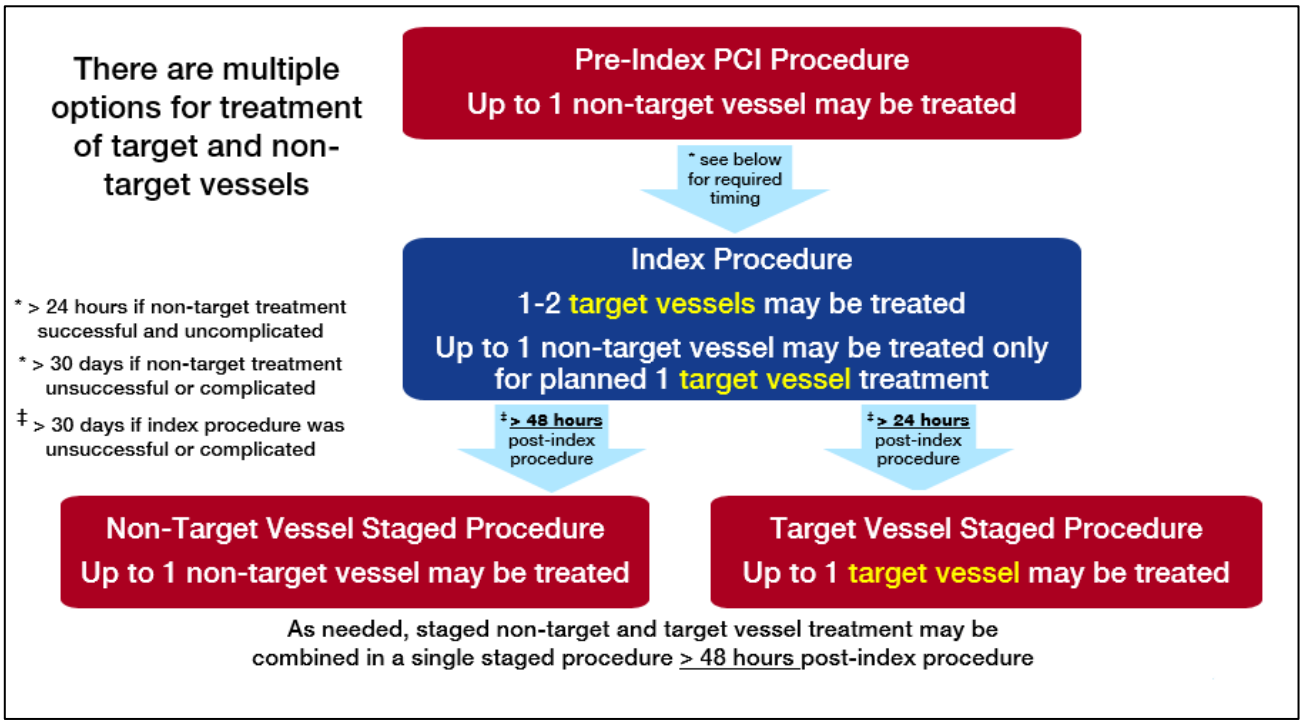


Figure 12. 3-Vessel Disease Treatment: 2 Target Vessels / 1 Non-Target Vessel.

6.5.4 Post procedure

All patients must have either a troponin level and/or a CKMB level (CK-MB preferred) drawn at 6-10 hours post PCI. The same biomarkers as those drawn at baseline should be assessed post-PCI. If the results are abnormal (>upper limits of normal), regardless of clinical significance, or if any procedural complications developed (temporary or sustained TIMI flow <III (visually assessed) in any vessel, or dissection ≥ NHLBI type B, or perforation, or prolonged ST-segment elevation or depression (>5 minutes), or cardiac arrest or need for defibrillation or cardioversion or hypotension /heart failure requiring mechanical or intravenous hemodynamic support or intubation), a second post-PCI troponin level and/or CK-MB level must be drawn at 6-10 hours after the first post-PCI biomarker draw or at discharge. In the event of high sensitivity troponin use (which is not recommended), an elevation of <7X ULN in the first (6-10 hr) post-PCI blood draw will not require an additional level, unless any procedural complications developed.

At least one 12-lead ECG must be performed within 24 hours post PCI in all patients.

A serum creatinine level must be drawn the calendar day after PCI or before discharge, whichever is earlier. If the subject develops contrast induced nephropathy (defined as an increase in serum creatinine ≥25% or an absolute increase of ≥0.5mg/dl (44.2µmol/L)), regardless of clinical significance, it is recommended that serial creatinine levels be drawn daily until the peak is reached and the creatinine is decreasing.

A serum hemoglobin must also be drawn the calendar day after PCI or before discharge, whichever is earlier. If the subject develops overt bleeding, or the hemoglobin level has fallen more than 3 g/dL (30 g/L) in the absence of overt bleeding, serial hemoglobin levels must be drawn at least daily until a nadir is reached or the hemoglobin level has stabilized.

The following considerations apply to subjects having staged procedures:

- The protocol required post-procedure serum creatinine, cardiac enzyme and 12-lead ECG assessments must be repeated for the staged procedure as done for the original index procedure.
- The follow-up regimen of aspirin and P2Y12 receptor inhibitor (dosage requirements and timing) must be maintained following the staged procedure as done for the original index procedure.
- The follow-up period is considered as having begun upon completion of the original index procedure.

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. Aspirin must be continued indefinitely. DAPT must be continued for at least 6 months in patients with stable CAD and for at least 12 months in patients who presented with acute coronary syndrome unless the patient is also taking chronic oral anticoagulation in which case a shorter duration of DAPT may be prescribed per local standard of care. Post-procedural medication use should not vary according to randomization assignment.

6.5.5 Scheduled Follow-ups

All patients enrolled in the study will be followed with clinic visit or phone calls at 30 (±7) days, 1 year (±30 days) and 2 years (±30 days) by the authorized study personnel at the study site.

- 30-day Follow-Up

Telephone or clinic visit follow-up at 30 days (± 7 days) including:

- Adverse events, medications, laboratory tests and 12-lead ECGs (if performed)

- 12 Month Follow-Up

Telephone or clinic visit follow-up at 12 months (± 30 days) including:

- Adverse events, medications, laboratory tests and 12-lead ECGs (if performed)

- 24 Month Follow-Up

Telephone or clinic visit follow-up at 24 months (± 30 days) including:

- Adverse events, medications, laboratory tests and 12-lead ECGs (if performed)

6.6 Patient Reported Outcome (PRO) Measures

The Study Coordinator or designee will administer patient-reported outcome questionnaires. It is important the subject understands the meaning of all words and instructions in the questionnaires. The subject should be instructed to ask any questions about the questionnaires if further explanation is needed. Once the questionnaires are completed, the Study Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

The following PRO measures will be collected according to the study requirements.

- EuroQoL 5D (EQ-5D-5L) to assess Overall Health Status in hospital (required at baseline, optional post-procedure), and at 30 day, 12 month and 24 month follow-up

6.7 Unscheduled Visits

Any patient, who develops cardiac symptoms or a major adverse cardiac event during the follow-up period should be evaluated by the investigator by telephone contact or clinic visit as deemed appropriate.

Requisite data are listed:

- Adverse events, medications, laboratory tests and 12-lead ECGs (if performed)

For any occurrence during follow-up of an ADE/SAE or potential TVF or MACE event, detailed records of that event, including but not limited to hospitalization records (admission record, discharge summary, catheterization and operative reports, and other supporting data as required) must be collected and sent to the Sponsor. Any follow-up angiograms and OCT imaging studies must be sent to the core laboratory for analysis.

For all randomized patients returning to the enrolling institution during the follow-up period with a cardiac event that requires cardiac catheterization, OCT imaging should be conducted at the time of the catheterization in the target vessel coronary distributions (both in the OCT-guided and angiography-guided patients). A three-vessel angiogram should also be performed. These studies must be submitted to the core laboratory for analysis. These additional steps should never unduly jeopardize patient safety. If a patient develops any TVF or MACE event, or requires repeat hospitalization or repeat angiography following the index catheterization, these events must be documented in the eCRF. Copies of charts, lab values, examinations and a copy of the angiogram and all diagnostic procedures performed (e.g. OCT) must be submitted to the Sponsor.

6.8 Schedule of Events

Assessment	Baseline/ Procedure	Procedure (Randomized to OCT)	Procedure (Randomized to Angiography)	Post-Procedure (<24 hours)[10]	30 Day (±7 days)[7]	12 Month (±30 days)[7]	24 Month (±30 days)	Unscheduled Visit[11]
Demographics and Medical History	X							
Physical Exam	X							
Pregnancy Test [1]	X							
12 Lead ECG	X			X				
Syntax score [2]	X							
Serum Creatinine	X [3]			X [6]				
Hemoglobin	X [3]			X [6]				
Troponin or CK-MB	X [4]			X [5]				
Angiogram	X							
Pre-PCI OCT		X						
PCI		X	X					
Post-PCI OCT		X	X [8]					
Cardiac Medications	X			X	X	X	X	X
Adverse Event		X	X	X	X	X	X	X
EQ5D	X[9]			X[9]	X	X	X	

[1] For women of childbearing potential
[2] Not required for subjects with single-vessel or simple 2-vessel disease
[3] Serum Creatinine and hemoglobin within 1 week prior to PCI.
[4] Baseline Troponin level or CK-MB: this may be drawn from the vascular sheath prior to PCI in subjects with stable coronary artery disease; labs must be drawn within 48 hours prior to PCI
[5] Post-Procedure Troponin level or CK-MB to be drawn at: 1) 6-10 hours post PCI; 2) if the first post-PCI biomarker is abnormal (>upper limits of normal), or if any procedural complications developed (see **Section 6.5.4** for details), a second post-PCI troponin level and/or CK-MB level must be drawn at 6-10 hours after the first post-PCI biomarker draw or at discharge. In the event of high sensitivity troponin use (which is not recommended), an elevation of <7X ULN in the first (6-10 hr) post-PCI blood draw will not require an additional level, unless any procedural complications developed.
[6] Post-Procedure creatinine and hemoglobin to be drawn at the calendar day post PCI or at discharge, whichever is earlier
- If the first creatinine draw indicates contrast induced nephropathy (absolute increase >0.5mg/dl (44.2µmol/L) or >25% or the pre-procedure value) it is recommended that creatinine be drawn daily until the peak is reached and the creatinine is decreasing. If the subject develops overt bleeding, or the hemoglobin level has fallen more than 3 g/dL (30 g/L) in the absence of overt bleeding, serial hemoglobin levels must be drawn at least daily until a nadir is reached or the hemoglobin level has stabilized.

[7] Office visit or Telephone when last subject enrolled reached 12-month follow-up, excluding subjects with follow-up completed within 30 days
[8] Blinded
[9] Required at baseline in subject in whom randomization is likely or definite, optional at post-procedure
[10] Roll-In subjects are followed through post-procedure visit
[11] For unscheduled visits, procedure details, tests and medications will not be recorded in the database

6.9 Health Care Economic Data Collection

Data on cardiovascular-specific resource utilization and will be collected prospectively for the index hospitalization and the full follow-up period using standardized case report forms. Procedural costs will be assessed using a resource-based approach to convert standard measures such as procedural duration and device utilization (e.g., stents, balloons, guidewires, etc.) into costs. Other hospital costs will be assessed using an "event-driven" approach in which specific complications and outcomes are assigned standard costs based on external data. Additional costs will be assigned for follow-up hospitalizations and repeat revascularization procedures, emergency room visits, outpatient diagnostic testing, and cardiovascular medications. In each case, costs will be assessed from the perspective of the U.S. healthcare system.

Cost and quality of life data will be used to perform a cost-effectiveness analysis from the perspective of the U.S. healthcare system.

6.10 Description of Activities Performed by Sponsor Representatives

The Sponsor is responsible for selecting qualified investigators, obtaining a signed investigators' agreement, and providing them with the information needed to conduct the investigation properly, ensuring the protection of human patients enrolled in the study, and identifying and distributing significant new information relevant to the investigation to the investigators. The Sponsor will evaluate circumstances where an investigator deviates from the CIP, and will retain the right to remove either the investigator or the investigational site from the study.

Trained Sponsor personnel will provide technical expertise and technical guidance on the use of the OPTIS system and Dragonfly Catheter, including training and proctored case coverage, as appropriate.

While Sponsor representatives may perform these activities, the Principal Investigator remains responsible for ensuring all clinical investigation data is collected as required per CIP.

6.11 Subject Study Completion

Subject participation in the clinical investigation will conclude upon completion of the 24-month visit. Upon completion of subject participation in the clinical investigation, the subject will return to standard of care.

6.12 Subject Withdrawal

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. Subjects will be requested to specify the reason for the request to withdraw. The investigator must make all reasonable efforts to retain the subject in the clinical investigation until completion of the clinical investigation.

In case of subject withdrawal, the site should make attempts to schedule the subject for a final study visit. At this final study visit, the subject will undergo the following assessments:

- Adverse events, medications, laboratory tests and 12-lead ECGs (if performed)

A subject will be considered 'Lost to Follow-up' after 2 consecutive missed visits and a minimum of two unsuccessful phone calls from investigational site personnel to the subject or contact to schedule the next follow-up visit. These two phone calls must be documented in the subject records. If the subject is deemed lost to follow-up a letter must be sent to the subject's last known address or to the subject's general

practitioner (GP) or family physician and a copy of the letter must be maintained in the subject's hospital records.

6.13 Study Committees

6.13.1 Steering Committee (SC)

A Steering Committee will advise the Sponsor on key aspects related to the development, execution, analysis and reporting, and overall conduct of the clinical investigation. A Steering Committee charter will define membership of the committee and outline the purpose, roles, responsibilities, and general rules of operation for the Steering Committee. This charter is maintained by the Sponsor and sets forth the procedures for the implementation of the Steering Committee.

6.13.2 Publication Committee (PC)

A Publication Committee shall be established to oversee study publications. Publication Committee membership may include members of the Steering Committee, investigators, representative(s) of Abbott and statisticians. The Publication Committee will be responsible for identifying, selecting and approving publication proposals and determining authorship according to a Publication Plan. A Publication Committee charter will define membership of the committee and outline the roles and responsibilities of the committee, as well as rules to define authorship.

6.13.3 Data Safety Monitoring Board (DSMB)

An independent DSMB will review on a regular basis accumulating data from the clinical investigation and will advise the Sponsor regarding the continuing safety of subjects and those yet to be recruited, as well as the continuing validity and scientific merit of the clinical investigation. DSMB members will not be investigators in the clinical investigation. At any time during the investigation, the DSMB may offer opinions or provide formal recommendations concerning aspects of the study that impact subject safety (e.g. safety-related protocol changes or input regarding study-related adverse event rates).

All events associated with the baseline imaging and or stenting procedure will be reported to the Data and Safety Monitoring Board (DSMB) and reviewed on a regular basis. The DSMB may request additional information as needed. Based on safety data, the DSMB may recommend to the Sponsor and Steering Committee to stop or otherwise modify the study. The Sponsor will make the final decision after weighing the recommendation of the DSMB whether the study should then be stopped, modified or continued without change. The DSMB procedures will be described in the DSMB Charter.

The primary function, responsibilities and membership of the DSMB will be described in detail in a DSMB charter.

6.13.4 Clinical Events Committee (CEC)

An Independent Clinical Events Committee (CEC) will be established and will be comprised of interventional and/or non-interventional cardiologists who are not participants in the study and are independent from the study. The CEC will review death, MI, stent thrombosis, repeat revascularizations, and intra-procedural complications (to determine their relationship to the imaging catheter). The CEC will also adjudicate the coronavirus disease 2019 (COVID-19) relatedness of a clinical endpoint event. The Committee procedures will be specified in the CEC charter.

7 Statistical Considerations

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

7.1 Endpoints

7.1.1 Primary Endpoint of MSA and Hypothesis

The primary endpoint of MSA is Post-PCI MSA measured by OCT in each randomized arm, as measured at the Cardiovascular Research Foundation OCT Core laboratory, which is blinded to imaging modality assignment.

Let M(OCT) be the mean MSA in OCT-guided arm, while M(Angio) is mean MSA in angiography-guided arm. The following hypothesis will be tested:

H_0: M(Angio) - M(OCT) ≥ 0

H_1: M(Angio) - M(OCT) < 0

The null hypothesis will be tested at the one-sided 2.5% significance level [redacted]

7.1.1.1 Analysis Methodology

[redacted]

7.1.1.2 Sample Size Determination

[redacted] a sample size of 1600 randomized subjects will provide at least 95% power to demonstrate superiority of treatment.

7.1.1.3 Analysis Population

The primary endpoint of MSA will be tested in all randomized subjects in whom one or more stents were implanted at a target lesion. Subjects who were randomized but in whom a stent was not implanted at a target lesion will be excluded.

7.1.2 Primary Endpoint of TVF and Hypothesis

The co-primary effectiveness endpoint is the rate of target vessel failure (the composite of cardiac death, target vessel MI (per primary protocol definition [see Appendix B]) and ischemia-driven target vessel

revascularization) at 2 years. For patients with multiple target vessels, TVF in either or both target vessels constitutes an endpoint event.

The following hypothesis will be tested for the analysis on TVF.

H_0: H(OCT) / H(Angio) ≥ 1

H_1: H(OCT) / H(Angio) < 1

where H(OCT) and H(Angio) are hazard function for the OCT-guided arm and angiography-guided arm. The null hypothesis will be tested at the one-sided 2.5% significance level.

[redacted]

7.1.2.1 Analysis Methodology

[redacted]

7.1.2.2 Sample Size Determination

[redacted] will provide 90% power at a one-sided significance level of 0.025, which is associated with approximately 2490 subjects. If an interim analysis indicates a sample size increase, the enrollment can be adjusted up to a total of 3656 subjects.

7.1.2.3 Analysis Population

The primary endpoint of TVF will be tested in all randomized subjects by intention-to-treat; subjects will be analyzed according to their randomized group regardless of the device attempted or implanted.

7.1.3 Major Secondary Endpoint of TVF Excluding Periprocedural MI and Hypothesis

The major powered secondary endpoint is the rate of target vessel failure excluding periprocedural MI (the composite of cardiac death, target vessel-related spontaneous MI or ischemia-driven target vessel revascularization). For patients with multiple target vessels, TVF excluding periprocedural MI in either or both target vessels constitutes an endpoint event.

The following hypothesis will be tested for the analysis on TVF excluding periprocedural MI.

H_0: H(OCT) / H(Angio) ≥ 1

H_1: H(OCT) / H(Angio) < 1

where H(OCT) and H(Angio) are hazard function for the OCT-guided arm and angiography-guided arm. The null hypothesis will be tested at the one-sided 2.5% significance level.

[redacted]

[redacted] a total sample size of 2490 subjects with 2-year follow-up will provide [redacted] approximately 85% power to reject the null hypothesis at a one-sided alpha of 2.5%.

7.1.3.1 Analysis Methodology

[redacted]

7.1.3.2 Analysis Population

The powered secondary endpoint of TVF excluding periprocedural MI will be tested in all randomized subjects by intention-to-treat; subjects will be analyzed according to their randomized group regardless of the device attempted or implanted.

7.2 Justification of Clinical Investigation Design

This is a prospective single-blind clinical investigation randomizing subjects between OCT-guided coronary stent implantation and angiography-guided coronary stent implantation. Subjects will be randomized in a 1:1 ratio. There are two primary endpoints of the study. The primary imaging endpoint is the acute post-procedural MSA (per target lesion basis) by OCT-guided-PCI compared to angiography-guided PCI. The MSA is a rationale primary endpoint as the most consistent and strongest parameter to predict clinical outcomes is the post-PCI MSA.[10-18] In the present study, after 1600 randomized subjects are enrolled with procedure completed, the primary endpoint of MSA will be tested to compare OCT-guided and angiography-guided arms and reviewed by the DSMB . If significantly larger MSA in OCT-guided arm is demonstrated, the DSMB will recommend that the trial will continue enrolling subjects (and the data will be kept blinded). Otherwise the acute OCT data will be unblinded to the Steering Committee and a decision will be made whether to stop the trial for futility, considering all imaging data available. No imaging data will be made public unless the trial is terminated prematurely for futility. Similarly, the Steering Committee will not be unblinded to any clinical data unless the decision is made to stop the trial prematurely.

The primary clinical endpoint is target vessel failure (cardiac death, TV-MI, or ischemia-driven TV-revascularization). TVF is a rationale co-primary endpoint as it is a clinical outcome which directly links the treatment effect to long-term clinical outcomes.

7.3 Overall Sample Size

The sample size required for evaluation of the first primary endpoint of MSA is 1600 randomized subjects, while the sample size for the primary endpoint [redacted] (approximately 2490 subjects). If an interim analysis suggests a sample size increase, up to a maximum of 3656 subjects will be randomized.

7.4 Timing of Primary Endpoint Analysis

There will be two analyses planned in the trial. The interim analysis of MSA will be conducted when 1600 randomized subjects are enrolled with procedures completed. If the superiority in the OCT-guided arm is demonstrated, the second analysis of TVF will be implemented when the pre-specified number of adjudicated TVF events are reached.

7.5 Success Criteria

The trial has two primary endpoints for MSA and TVF to compare the effectiveness of the OCT-guided PCI against the angiography-guided PCI. Both primary endpoints must be met in order to claim the study success.

7.6 Interim Analysis

[redacted]

7.7 Multiplicity Adjustment

[redacted]

7.8 Sensitivity Analyses

[redacted]

As referenced in **Section 5.3.3**, the impact of the SCAI definition of periprocedural MI will be reported as sensitivity analyses at 30 days, 1 year and 2 years for the endpoints TV-MI$_{SCAI}$, Periprocedural MI$_{SCAI}$, All MI$_{SCAI}$ and TVF$_{SCAI}$.

Sensitivity analyses for the primary and major secondary endpoints will be performed by removing the impact of COVID-19 if applicable. Details are provided in the SAP.

7.9 Statistical Criteria for Termination

[redacted]

7.10 Deviations from Statistical Plan

If any deviations from the original statistical plan occur, such deviations will be documented in the clinical study report or statistical report containing the analysis results.

8 Risks and Benefits

The risk analysis included an objective review of published and available unpublished medical and scientific data. The sections below provide an overview of residual risks identified in the risk management report and anticipated benefits of the medical device. The risks associated with the Dragonfly Imaging Catheter can be found in the Instructions for Use.

8.1 Risks Associated with the Study Devices

The risks involved in vascular imaging include those associated with all catheterization procedures. The following complications may occur as a consequence of intravascular imaging and may necessitate additional medical treatment including surgical intervention.

- Allergic reaction to the contrast media or drug administered for the procedure
- Bleeding
- Arterial dissection, injury, or perforation
- Abnormal heart rhythm or arrhythmias
- Unstable angina
- Coronary artery spasm
- Thrombus formation, abrupt closure, or total occlusion
- Embolism
- Myocardial ischemia
- Acute myocardial infarction
- Repeat revascularization
- Renal insufficiency or failure from contrast media use
- Death
- Potential Adverse events:
    - Catheter access site reactions: sterile inflammation or granuloma
    - Tissue necrosis

In the St. Jude Medical prospective multi-center study, under a significant risk IDE application, one (1/59, 1.7%) subject had a serious adverse event which was judged by the DSMB to be related to the procedure but not the device. No subjects died during the clinical study. One (1/59, 1.7%) subject had a device-related adverse events which was sinus bradycardia although this event was not determined to be serious. In the ILUMIEN III:OPTIMIZE PCI study, procedural major adverse events were not different between intracoronary imaging (OCT and IVUS) and angiography guidance.[19] The use of OCT requires additional contrast media which may potentially increase the risk of acute kidney injury, but there were no occurrences of acute renal failure ILUMIEN III study.[19] Since the devices are currently on the market, the risk profile is known and the risk/benefit ratio is reasonable for this study.

Observed and potential adverse events occurring with the XIENCE family of stents are listed in the IFUs. The incidence of these adverse events is comparable to other PCI devices. There may be risks related to the device that are unknown at present.

8.1.1 Residual Risks Associated with Study Devices

Possible adverse events associated with the introduction of an imaging catheter are: dissection, thrombosis, distal embolization, abrupt closure of the vessel, rupture, bleeding, coronary artery spasm, myocardial ischemia or infarction, unstable angina and cardiac arrhythmias.
Possible adverse events associated with additional use of contrast media or drugs administered during the procedure: allergic reaction, renal insufficiency or failure. Other potential adverse events associated with the catheter insertion site are sterile reactions, inflammation, granuloma-formation or tissue necrosis.

The XIENCE Risk Assessment Report utilizes the Failure Modes and Effects Analysis (FMEA) tool to systematically identify potential hazards associated with the process, design, components, and use of the XIENCE product family. Based upon preclinical, clinical, bench data, and commercial post-production data, all residual risks are appropriate and acceptable.

8.2 Risk Control Measures

Every possible effort will be taken to minimize the risks, including:

- Careful selection of experienced Investigators for the clinical investigation
- Adequate monitoring for clinical investigation sites
- Conducting the clinical investigation in accordance with the CIP, all applicable laws and regulations and any conditions of approval imposed by the appropriate IRB/EC or applicable regulatory authorities where the clinical investigation is performed
- Preparation of the 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 both on the CIP and the OPTIMIZE PCI algorithm.
- Futility analysis will be conducted to limit exposure of subjects to an ineffective procedure

  All events associated with the baseline imaging and or stenting procedure will be reported to the Data and Safety Monitoring Board (DSMB) and reviewed on a regular basis. The DSMB may request additional information as needed. Based on safety data, the DSMB may recommend to the Steering Committee to stop or otherwise modify the study. The Steering Committee will make the final decision after weighing the recommendation of the DSMB whether the study should then be stopped, modified or continued without change. The DSMB procedures will be described in the DSMB Charter.

8.3 Possible interactions with concomitant treatments

No interaction with concomitant treatment is anticipated.

8.4 Anticipated Benefits

Additional imaging with OCT may benefit patients enrolled in the study. The knowledge of vessel diameter and lesion characteristics will help to choose the correct stent size and to optimize implantation which in turn can reduce stent thrombosis and prevent in-stent restenosis. Also, in the OCT arm, post stenting imaging allows to detect and treat sub optimal results, such as edge dissections, tissue protrusion, malapposition or under-expansion. Stent optimization may lead to better clinical outcome.

8.5 Risk-to-Benefit Rationale

The excellent safety profile of XIENCE family of stents has been well demonstrated. Comprehensive analysis of product level clinical data, including clinical trial, post-marketing, and literature data, confirms that any undesirable risks identified are outweighed by the clinical benefits of XIENCE. Stent optimization with OCT use may lead to better clinical outcome. All procedures required by the protocol are conducted according to current clinical practice, and participation in this trial carries no additional risk to the patient. Since the devices are currently on the market and considering the risk profile described above and the potential benefits, the risk/benefit ratio is reasonable for this study.

8.6 History of Device Modifications or Recall

There have been no modifications or recall in relation to safety and clinical performance of the devices to be used in this study.

9 Requirements for Investigator Records and Reports

9.1 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 Adverse Events

To comply with worldwide standards and guidelines on clinical trial adverse event reporting, Abbott Vascular has developed uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

10.1 Definitions

10.1.1 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.

Note 1: This definition includes events related to the medical device 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.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical device, whether or not related to the medical device.

10.1.2 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 that either:
    1) Resulted in a life-threatening illness or injury, or
    2) Resulted in a permanent impairment of a body structure or a body function, or
    3) Required in-patient hospitalization or prolongation of existing hospitalization, or
    4) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
    5) Resulted in chronic disease
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.
Note 2: 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.

10.1.3 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.

10.1.4 Device Deficiency/Device Malfunction

Device deficiency (DD) 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 (DM) 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 the trial protocol.

10.1.5 Unanticipated (Serious) Adverse Device Effect

Unanticipated (serious) adverse device effect [U(S)ADE] refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.2 Safety Reporting

Safety surveillance and reporting starts as soon as the patient is randomized (or included as a roll-in subject) in the clinical investigation. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation or the subject withdraws from the clinical investigation.

Adverse event data 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.

For the purposes of this investigation the following adverse events will be reported:

- All serious adverse events
- All device and procedure-related adverse events
- Unanticipated (serious) adverse device effects

In addition, the following adverse events regardless of seriousness or relatedness will be collected:

- Myocardial infarction
- Revascularization
- Stent thrombosis

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported. Non-cardiac related abnormal laboratory values will not be considered AEs unless:

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

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 above.

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.

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.

Additional information may be requested by the Sponsor in order to support the reporting of AEs to regulatory authorities. The investigator must notify the IRB/EC, if appropriate, in accordance with national and local laws and regulations, of the AEs reported to the Sponsor.

10.2.1 Unanticipated Serious Adverse Device Effect Reporting to Sponsor and EC

Abbott Vascular requires the Investigator to report any USADE to the sponsor within 3 calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the EC per EC requirements.

10.2.2 Device Deficiency/Device Malfunction Reporting

All device deficiencies/malfunctions should be reported within the EDC System on the appropriate eCRF form. A fax 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. 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 fax form.

The investigator should report all DDs/DMs to the Sponsor as soon as possible but no later than outlined below:

Trial sites	Reporting timelines
All Sites	DDs/DMs must be reported no later than 3 calendar days from the day the trial personnel became aware of the event or as per the trial site's local requirements, if the requirement is more stringent than those outlined.

The device, if not implanted or not remaining in the subject, should be returned to Abbott Vascular.

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

10.2.3 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor or designee will report the SAEs and DDs/product experiences (PEs) to the country regulatory authority, per local requirements.

10.3 Safety Monitoring by Data Safety Monitoring Board (DSMB)

The DSMB will serve in an advisory role to Abbott Vascular to ensure safety by reviewing cumulative data from the clinical trial at prescribed intervals for the purpose of safeguarding the interests of trial participants.

The DSMB may consider a recommendation for modifications or termination of the trial based on any perceived safety concerns regardless of statistical significance. The recommendations of the DSMB are not binding, and all final decisions related to trial modifications rest with Abbott Vascular.

10.4 Source records

Source documents will be created and maintained by the investigational site team throughout the clinical investigation. The data reported on the CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

10.5 Records Retention

The Sponsor and the Principal Investigators will maintain the clinical investigation documents as required. Measures will be taken to prevent accidental or premature destruction of these documents. The Principal Investigator or the Sponsor may transfer custody of records to another person/party and document the transfer at the investigational site or the Sponsor's facility, as appropriate.

The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

All original source documents must be stored for the maximum time required by the regulations at the hospital, research institute, or practice in question. If original source documents can no longer be maintained at the site, the investigator will notify the Sponsor.

11 Clinical Data Handling

The Sponsor will be responsible for the data handling. The Sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies. Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations worldwide and/or any other worldwide regulatory authority in support of a market-approval application.

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, database cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the clinical investigation duration. All revisions will be tracked and document controlled.

Subject data will be captured in a validated electronic data capture (EDC) system hosted by the Sponsor.

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.

11.3 Document and Data Control

11.3.1 Traceability of Documents and Data

The investigator will ensure accuracy, completeness legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

11.3.2 Recording Data

The CRF will be completed by the authorized site personnel. An appropriate comment will be provided to explain changes to data reported on the CRF.

12 Monitoring

It is the responsibility of the Sponsor to ensure the clinical investigation is conducted, recorded and reported according to the approved CIP, subsequent amendment(s), applicable regulations and guidance documents.

Monitoring will be conducted according to the Sponsor's Clinical Monitoring work instruction. Prior to beginning the clinical investigation, the Sponsor will contact the investigator or designee to discuss the

clinical investigation and data requirements. A designated monitor will periodically review the subject records and associated source documents. The investigator shall make subject and clinical investigation records available to the clinical monitor for monitoring.

Centralized monitoring will occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential CIP deviations that may be indicative of site non-compliance.

13 Compliance Statement

13.1 Statement of Compliance

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812 and OUS ISO14155:2011) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the respective investigational site and by the applicable regulatory authorities (e.g., FDA, PMDA, MHRA, etc.).

The investigator will sign a Clinical Trial or Investigator Agreement and agrees to be compliant with it. The investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining IRB/EC approval and relevant Regulatory Authority approval, if applicable, and authorization from the Sponsor in writing for the clinical investigation. If additional requirements are imposed by the IRB/EC or relevant Regulatory Authority, those requirements will be followed. If any action is taken by an IRB/EC or a relevant Regulatory Authority with respect to the clinical investigation, that information will be forwarded to the Sponsor.

The Sponsor has taken up general liability insurance in accordance with the requirements of the applicable local laws. An appropriate Sponsor's country representative will be utilized to understand the requirements for the type of insurance that will be provided for subjects, and such information will be incorporated into the site informed consent, as applicable. If required, additional subject coverage or a clinical investigation specific insurance will be provided by the Sponsor.

13.2 Quality Assurance Audits and Regulatory Inspections

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.

The Principal Investigator or institution will provide direct access to source data during and after the clinical investigation for monitoring, audits, IRB/EC review and regulatory authority inspections, as required. The Principal Investigator or institution will obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical investigation.

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.

13.3 Repeated and Serious Non-Compliance

In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the Sponsor, a monitor or designee will attempt to secure compliance by one or more of the following actions:

- Visiting the investigator,
- Contacting the investigator by telephone,
- Contacting the investigator in writing,
- Retraining of the investigator.

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical investigation, the Sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical investigation. In case of termination, the Sponsor will inform the responsible regulatory authority, as required, and ensure that the IRB/EC is notified, either by the Principal Investigator or by the Sponsor.

14 Suspension or Premature Termination of the Clinical Investigation

The Sponsor reserves the right to terminate the clinical investigation at any stage, with appropriate written notice to the investigators, IRB/ECs and relevant Regulatory authorities, if required.

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:

- Unanticipated adverse device effect (e.g., UADE) occurs and it presents an unreasonable risk to the participating subjects
- An oversight committee (e.g., Steering/Executive Committee, Data Monitoring Committee) makes a recommendation to stop or terminate the clinical investigation (such as higher frequency of anticipated adverse device effects)
- Further product development is cancelled.

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 return all clinical investigation materials (including devices) to the Sponsor, and provide a written statement to the IRB/EC (if applicable). All applicable clinical investigation documents shall be subject to the same retention policy as detailed in **Section 9.4** of the CIP.

A Principal Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in a clinical investigation at the investigational sites 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 investigational site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following up the subjects enrolled in the clinical investigation, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her investigational site, if appropriate.

15 Ethical Consideration

15.1 Institutional Review Board/Medical Ethics Committee Review and Approval

IRB)/EC 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/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements.

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

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

16 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.

17 Publication Policy

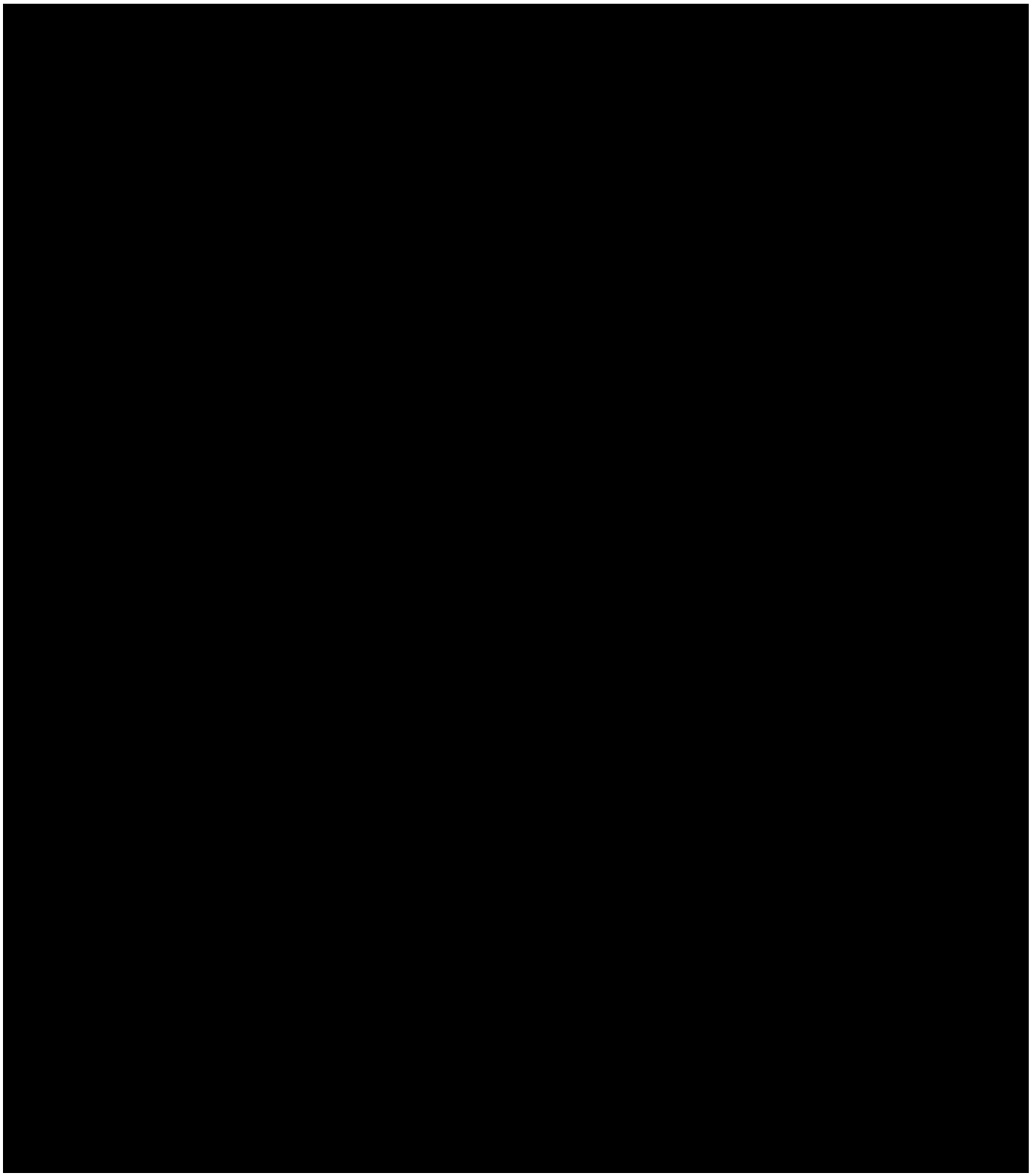
The data and results from the clinical investigation are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation. The Investigators will not use this clinical investigation-related data without the written consent 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.

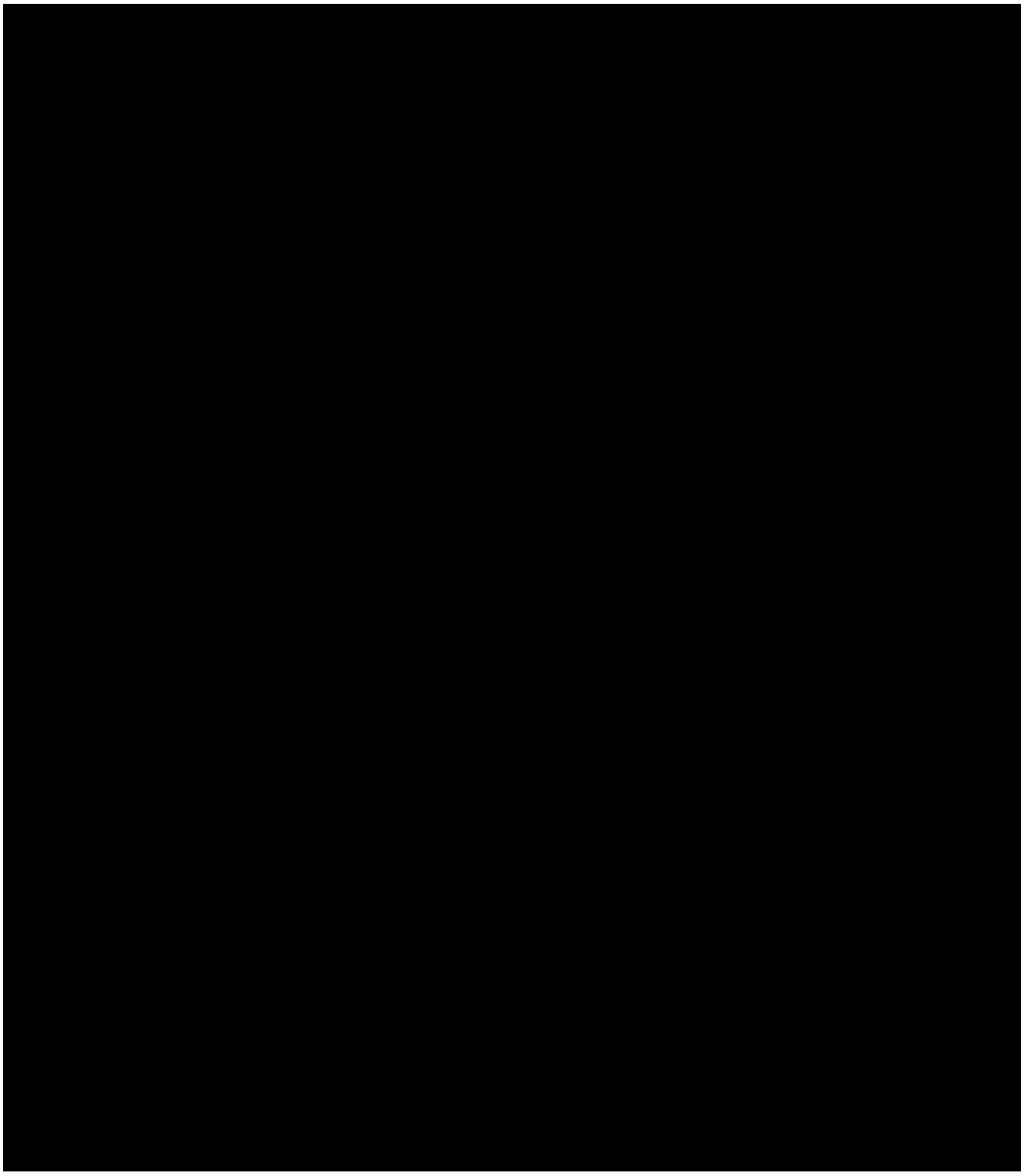
18 Reporting Results on ClinicalTrials.gov Website

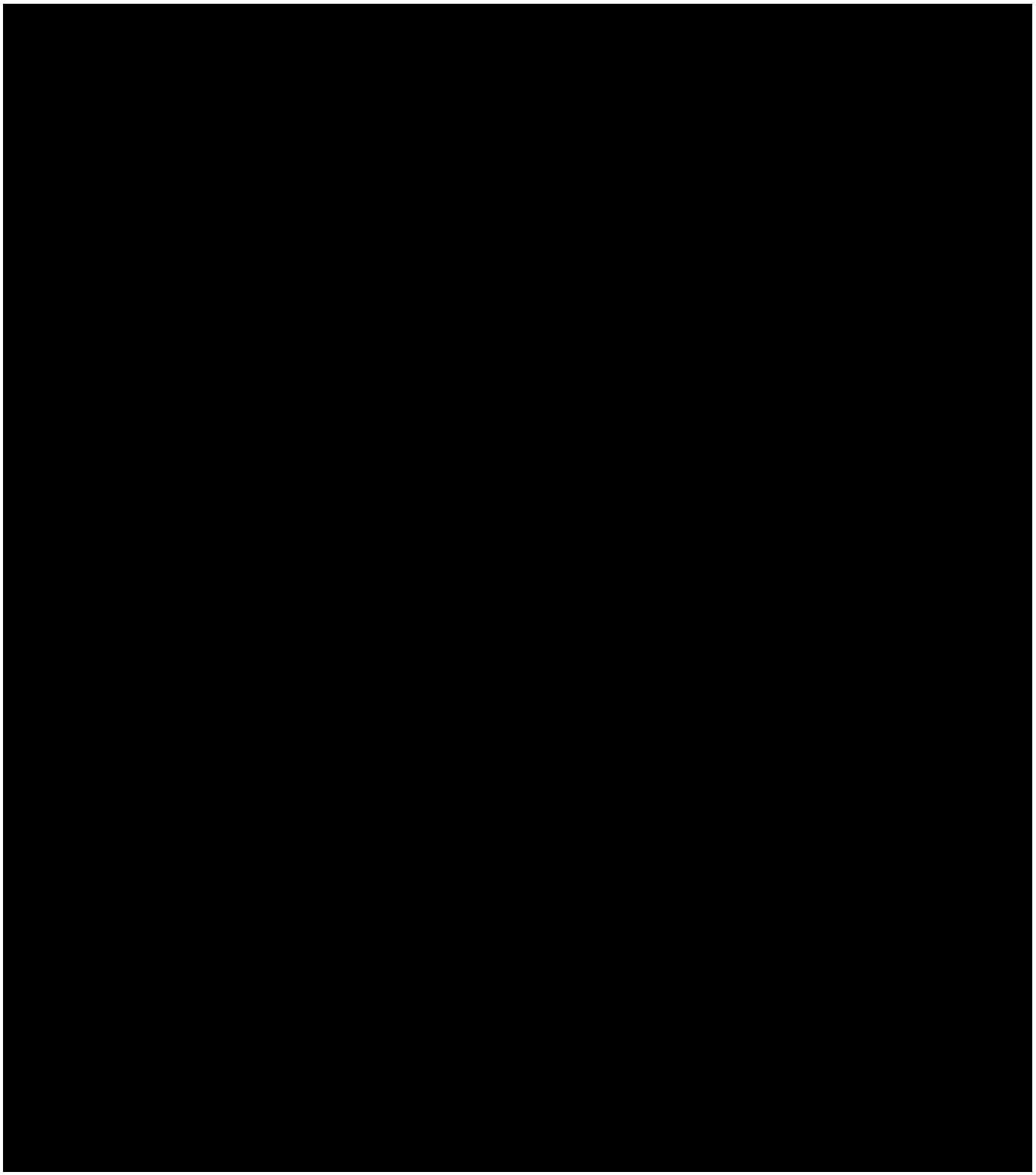
The Sponsor will register the clinical trial on www.clinicaltrials.gov, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. The Sponsor shall be responsible for any such registration and results posting as required by ClinicalTrials.gov. Investigational sites shall not take any action to register the trial. A full report of the pre-specified outcomes, including any negative outcomes, will be made public through the ClinicalTrials.gov website according to the requirements of Section 801 of the FDA Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through ClinicalTrials.gov website.

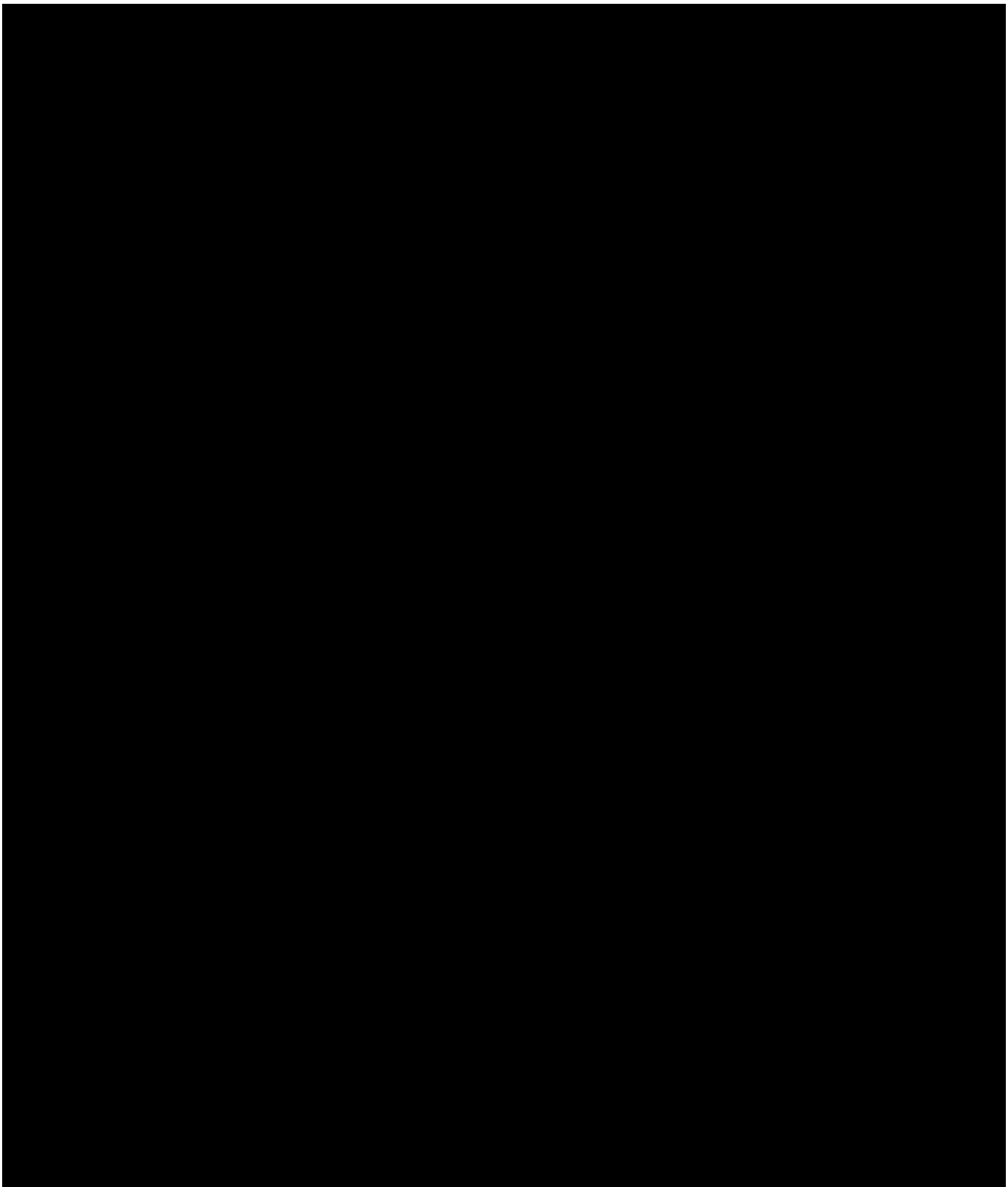
Appendix A: CIP Revisions

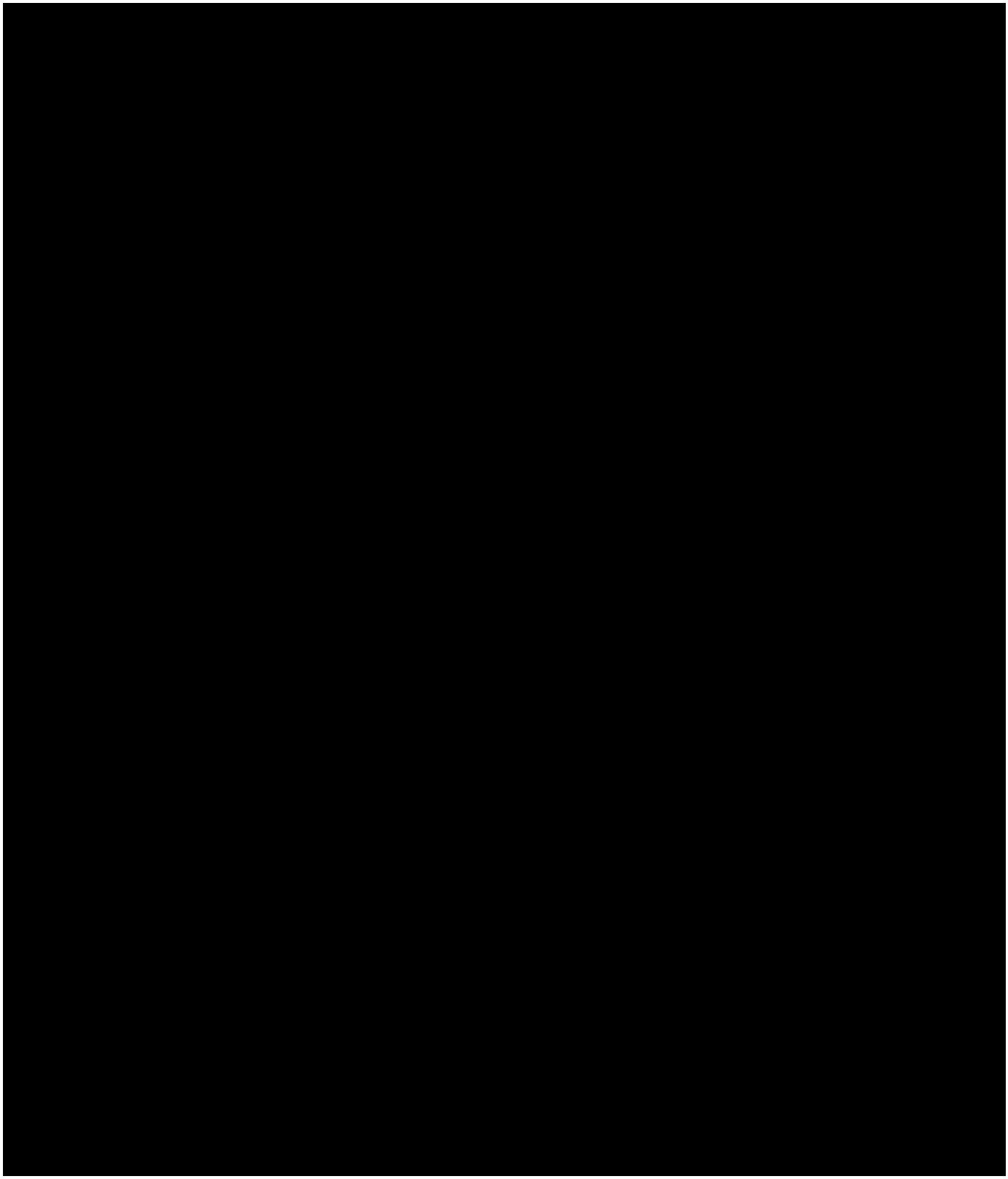
[redacted]

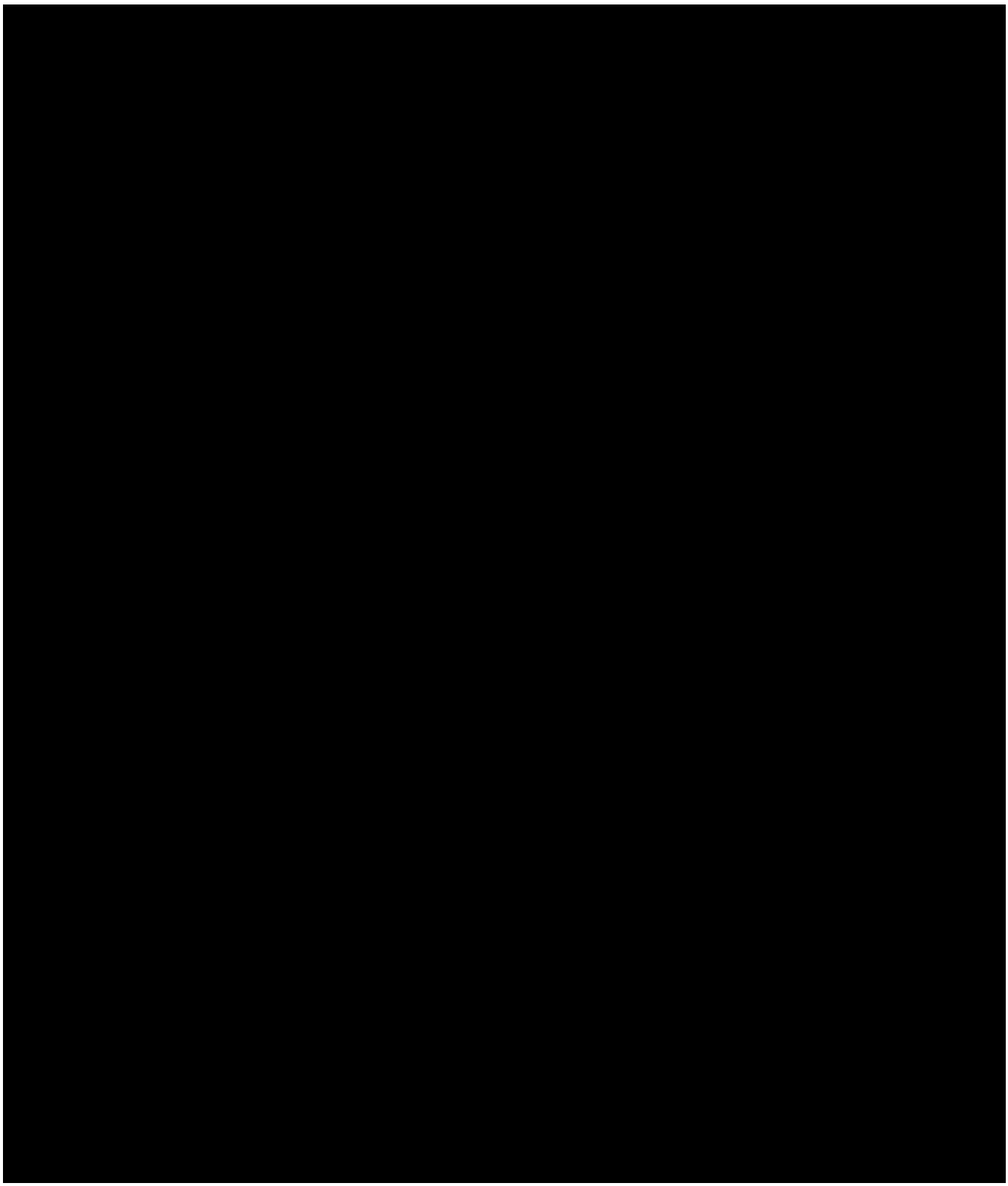












[redacted]

Appendix B: Definitions

Vulnerable Patient
Vulnerable patients are defined as patients whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

Abrupt Closure: Intraprocedural coronary occlusion associated with clinical evidence of myocardial ischemia.

Coronary Artery Embolism: Obstruction in the coronary artery due to an embolus such as, air, plaque, thrombosis or debris.

Chronic Total Occlusion (CTO): Lesions with thrombolysis in myocardial infarction (TIMI) 0 flow for ≥3 months.

Crossover: Crossover from one assigned treatment to the other is strongly discouraged.

De Novo Lesion: A native coronary artery lesion not previously treated.

Death (Per ARC Circulation 2007; 115: 2344-2351): All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac.

> **Cardiac death:**
> Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment.
>
> **Vascular death:**
> Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.
>
> **Non-cardiovascular death:**
> Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

Dissection:
Type 0: None
Type A: Small radiolucent area within lumen of the vessel
Type B: Linear, non-persisting extravasation of contrast
Type C: Extraluminal, persisting extravasation of contrast
Type D: Spiral shaped filling defect
Type E: Persistent lumen defect with delayed ante/retrograde flow
Type F: Filling defect accompanied by total arterial occlusion
(Note: Type A and B are generally considered benign and minor dissections)

Reference Vessel Diameter (RVD): Average diameter of proximal and distal healthy segments by QCA. "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 QCA).

Acute Gain: The difference between the post-PCI MLD and the pre-PCI MLD (as measured by QCA).

Percent Diameter Stenosis: The value calculated as 100 * (1 - MLD/RVD) using the mean values from two orthogonal views (when possible) by QCA.

Ischemic Episode: An inadequate flow of blood to a part of the body resulting from low oxygen in the blood or tissues, generally as a result of an obstruction of the arterial blood flow.

Killip Class*
Class I: No evidence of heart failure
Class II: Findings of mild to moderate heart failure (S3 gallop, rales < half-way up lung fields or elevated jugular venous pressure
Class III: Pulmonary edema
Class IV: Cardiogenic shock defined as systolic blood pressure < 90 and signs of hypoperfusion such as oliguria, cyanosis, and sweating.

Major Adverse Cardiac Event (MACE): The composite of cardiac death, myocardial infarction, and ischemia-driven target lesion revascularization.

Myocardial Infarction (Primary Protocol Definition)

Periprocedural MI – Modified ARC-2 Definition[20]
Periprocedural myocardial infarction occurring within 48 hours after all percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) procedures:[20]

Absolute rise (from baseline to within 48 hours of procedure) in cardiac troponin of ≥35x the 99th percentile URL (or ≥35x ULN if URL is not available) or in the absence of cardiac troponin, rise in CK-MB to ≥ 5x the 99th percentile URL (or ≥5x ULN if URL is not available). Note, cardiac troponin assessments are preferentially used if available; otherwise CK-MB may be used.

In addition, 1 (or more) of the following measures of myocardial ischemia must be present post-procedure:
- New significant Q waves (≥40 ms in duration and ≥1 mm deep in voltage in ≥2 contiguous leads) or equivalent
- Persistent flow-limiting angiographic complications in a major epicardial vessel or branch ≥1.5 mm in diameter present at the end of the PCI procedure (or during angiography performed to evaluate a post-CABG complication) as assessed at the angiographic core laboratory
- New substantial loss of viable myocardium on serial imaging

These assessments apply to patients: a) with baseline CK-MB or cardiac troponin levels ≤1x the 99th percentile URL (or ≤1x ULN if URL is not available); b) in whom the baseline biomarker is >1x the 99th percentile URL (or >1x ULN if URL is not available) and stable or falling; and c) with a single elevated

baseline draw who have a chronic coronary syndrome (CCS). In the latter two groups (patients in whom the baseline is elevated and stable or falling and CCS patients with a single elevated baseline draw), the post-procedural troponin (or CK-MB) must rise above the most recent baseline by an increment of the values above (i.e. for troponin ≥35x the 99th percentile URL (or ≥35x ULN if URL is not available) or in the absence of cardiac troponin, for CK-MB ≥5x the 99th percentile URL (or ≥5x ULN if URL is not available).

These assessments do not apply to patients: a) in whom baseline CK-MB or troponin levels are elevated and rising; and b) with a single elevated baseline level who presented with a NSTEMI or STEMI in whom it is uncertain whether the peak has been reached. In such patients periprocedural MI will only be adjudicated if the troponin (or CK-MB) biomarker increases from the prior measure by the increments above, and at least 2 of the 3 above criteria for myocardial ischemia are present.

Spontaneous MI

All MIs which are not peri-procedural are considered spontaneous MIs. Spontaneous myocardial infarctions are usually related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. However, spontaneous MIs can also be due to an imbalance between supply and demand, or due to stent thrombosis, graft occlusion or other causes. Most patients with spontaneous MI have underlying severe CAD but on occasion non-obstructive or no CAD. Spontaneous MIs usually occur beyond 48 hours post-procedure but can occasionally occur within 48 hours of a revascularization procedure if the cause is clearly distinct from the index procedure (e.g. a stent thrombosis at 24 hours). Spontaneous MIs are defined and subclassified according to types 1, 2, 3, 4b and 4c according to the 4th Universal Definition of MI classification[21] (below).

Spontaneous Myocardial Infarction: Fourth Universal Definition

Type 1: MI caused by atherothrombotic coronary artery disease (CAD) and usually precipitated by atherosclerotic plaque disruption (rupture or erosion) is designated as a Type 1 MI. Type 1 MI is characterized by detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy[13]

Type 2: Myocardial infarction secondary to an ischemic imbalance.
The pathophysiological mechanism leading to ischaemic myocardial injury in the context of a mismatch between oxygen supply and demand has been classified as type 2 MI. Type 2 MI is characterized by detection of a rise and/or fall of cTn values with at least one value above the 99th

[13] Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial haemorrhage, meets the type 1 MI criteria regardless of cTn values.

percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable. Patients are designated as having Type 3 MI who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Type 4b: Myocardial infarction related to stent thrombosis associated with percutaneous coronary intervention (PCI).
Myocardial infarction associated with stent thrombosis is designated as Type 4b MI, detected by angiography or autopsy using the same criteria utilized for Type 1 MI.

Type 4c: Myocardial infarction related to restenosis associated with percutaneous coronary intervention (PCI).
This PCI-related MI type is designated as Type 4c MI, defined as focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for Type 1 MI.

Periprocedural Myocardial Infarction (Secondary Definition)

As a sensitivity analysis, periprocedural MI will also be adjudicated and reported according to the SCAI Definition:

1. In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent left bundle branch block OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent left bundle branch block.

2. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.

3. In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

Myocardial Infarction Relation to Target Vessel:

Infarcts will be adjudicated according to anatomical origin based on review of coronary angiography performed at the time of the event. Those that cannot be clearly attributed to a particular vessel (target or non-target) either because the origin of the event on the angiogram is ambiguous or the angiogram was not performed will be considered as indeterminate vessel MI.

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.

No Reflow: After treatment, the Thrombolysis In Myocardial Infarction (TIMI) score is reduced to 1 or 0 in the absence of a severe focal mechanical obstruction (e.g., dissection). Persistent No Reflow is defined as a condition where the TIMI flow continues to be 1 or 0 even at the end of the procedure despite the use of adjunctive drugs or mechanical intervention for relief of vasospasm.

Perforation Classification:

Type I (Fully contained): Extraluminal crater without extravasation.

Type II (Limited extravasation): Pericardial or myocardial blush without contract jet extravasation.

Type III (Brisk extravasation): Extravasation through frank (≥1mm) perforation.

Cavity spilling: Perforation into an anatomic cavity chamber, coronary sinus, etc.

Procedural complications: Defined as A) angiographic core laboratory-assessed complications listed in Angiographic Endpoint 11(vi) occurring anytime during the procedure; or B) site-assessed prolonged ST-segment elevation or depression (>30 minutes), cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation, or procedural death.

Procedural success: Defined as A) angiographic core laboratory-assessed final (post-PCI) lesion angiographic diameter stenosis <30% and target vessel TIMI III flow without any of the angiographic complications listed in Angiographic Endpoint 11(vi); plus B) the absence of site-assessed prolonged ST-segment elevation or depression (>30 minutes), cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation, or procedural death.

OCT imaging-related procedural complications: Any procedural complications (e.g. angiographic dissection, perforation, thrombus, acute closure, etc.) requiring any active intervention (e.g. prolonged balloon inflations, additional stent implantation, pericardiocentesis, intubation, hemodynamic support or pressors, defibrillation or cardioversion) or death adjudicated by the CEC as definitely or likely attributable to the physical performance of OCT-imaging (e.g. passing the catheter through the vasculature or stent, or injecting contrast to clear the blood for imaging). For this definition, adverse events that arise due to changes in PCI strategy as the result of OCT findings are NOT considered OCT imaging-related procedural complications.

Principal Investigator: An individual who actually oversees and conducts a clinical investigation. In the event of an investigation being conducted by a team of individuals, "PI" refers to the responsible leader of the team.

Slow Flow: After treatment, the TIMI score is reduced to 2 or less in the absence of a severe focal mechanical obstruction (e.g., dissection). Persistent Slow Flow is defined as a slow flow condition present at the procedure end that is not resolved by adjunctive drugs or mechanical intervention for relief of vasospasm.

Severe Calcification:
By angiography: presence of radiopacities noted without cardiac motion prior to contrast injection usually involving both sides of the arterial wall in at least one (1) location, with total length of calcium (including segmented) ≥15 mm and extending partially into the target lesion.

By OCT: presence of ≥180° of calcium in at least one (1) cross section with minimal thickness >0.5mm.

Intraprocedural stent thrombosis: new or increasing thrombus developing within or adjacent to the stent during the index PCI procedure

Stent Thrombosis (definite or probable; modified ARC definitions):

Acute stent thrombosis (*): from completion of PCI procedure to 24 hours after stent implantation

Subacute stent thrombosis (*): >24 hours – 30 days after stent implantation

Late stent thrombosis (**): >30 days – 1 year after stent implantation

Very late stent thrombosis (**): >1 year after stent implantation

(*) acute or subacute can also be replaced by the term early stent thrombosis.
(**) including 'primary' as well as 'secondary' late stent thrombosis; 'secondary' late stent thrombosis is a stent thrombosis after a target lesion revascularization.

Stent Thrombosis, Definite*:
Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.

Angiographic confirmation of stent thrombosis
The presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent AND presence of at least 1 of the following criteria within a 48-hour
time window:

- Acute onset of ischemic symptoms at rest

- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)

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

Stent Thrombosis, Probable:
Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

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

Successful and Uncomplicated:
For non-target lesion treatment during the index procedure, defined as angiographic diameter stenosis <10% for all treated non-target lesions, with TIMI III flow in this vessel, without final dissection ≥ NHLBI type B, perforation anytime during the procedure, prolonged chest pain (>5 minutes) or prolonged ST-segment elevation or depression (>5 minutes), or cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation).

Target Lesion: The target lesion is the treated lesion starting 5mm proximal to the stented lesion and ending 5mm distal to the stented lesion.

Target Lesion Failure (TLF): The composite of cardiac death, target vessel related myocardial infarction, or ischemia-driven target lesion revascularization.

Target Lesion Revascularization (TLR): Repeat revascularization of the target lesion.

Target Vessel Failure (TVF): The composite of cardiac death, target vessel related myocardial infarction, or ischemia driven target vessel revascularization.

Target Vessel Revascularization (TVR): Repeat revascularization of the target vessel (inclusive of the target lesion).

Ischemia-Driven [ID] Revascularization (TLR/TVR): A revascularization is considered ischemia driven if associated with any of the following:

- Positive functional ischemia study including positive FFR, iFR, etc.
- Ischemic symptoms and angiographic diameter stenosis ≥50% by core laboratory QCA
- Angiographic diameter stenosis ≥ 70% by core laboratory QCA without angina or positive functional study

COVID-19 Relatedness Definitions
The COVID-19 relatedness to an adverse event, is adjudicated by the CEC committee into 3 categories: likely related, possibly related, or not likely related, based on the COVID-19 relatedness definitions that are described on the CEC charter. Please refer to the CEC charter for the COVID-19 relatedness definitions.

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 cineangiographic 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.

Thrombus, Nonocclusive: Intracoronary thrombus is defined as a (spheric, ovoid or irregular) non-calcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

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

Appendix C: Labels

[redacted]

Appendix D: Case Report Form

[redacted]

Appendix E: Informed Consent Form

[redacted]

Appendix F: Pre-specified Powered Analysis of XIENCE in the In-Stent Restenosis (ISR) Population

Introduction

Abbott is evaluating the safety and effectiveness of treating in-stent restenosis (ISR) lesions with the XIENCE family of stents within the ILUMIEN IV trial. The trial enrolls patients undergoing planned XIENCE stent implantation during a clinically indicated PCI procedure who satisfy the eligibility criteria described in **Section 5.4** of this CIP. A pre-specified powered analysis of XIENCE is being conducted in randomized ILUMIEN IV subjects with ISR and is described below. The XIENCE ISR analysis is intended to support an indication expansion for treatment of ISR lesions with the XIENCE family of stents in the USA.

The XIENCE ISR analysis is independent of the main ILUMIEN IV study objective outlined in **Section 1.1** of the CIP, which is to demonstrate the superiority of an OCT-guided stent implantation strategy as compared to an angiography-guided stent implantation strategy.

Objective

The objective of the XIENCE ISR analysis is to demonstrate the safety and effectiveness of XIENCE in the treatment of ISR lesions.

Analysis Population

The XIENCE ISR analysis population is comprised of randomized subjects pooled from both study arms and enrolled under the ILUMIEN IV regulated protocol [redacted] or the post-market protocol [redacted], who have had at least one XIENCE stent implanted in an ISR target lesion.

Endpoints

The primary endpoint for the XIENCE ISR analysis is target lesion failure (TLF_{ISR}). TLF_{ISR} is the event rate of the composite outcome of cardiac death, target vessel myocardial infarction (TV-MI) (per primary protocol definition [see Appendix B]), or ischemia-driven target lesion revascularization (ID-TLR), assessed at 1 year.

Non-powered secondary endpoints for the XIENCE ISR analysis to be assessed at 1 year are as follows:

1. Cardiac death $_{ISR}$
2. TV-MI_{ISR}
3. ID-TLR_{ISR}
4. Stent thrombosis $_{ISR}$
5. All-cause mortality $_{ISR}$

In addition, the following outcomes will be reported as sensitivity analyses at 1 year:

6. TV-$MI_{ISR,SCAI}$ (periprocedural MI by SCAI definition and spontaneous MI by protocol definition)
7. Periprocedural $MI_{ISR,SCAI}$ (by SCAI definition)
8. All $MI_{ISR,SCAI}$ (periprocedural MI by SCAI definition and spontaneous MI by protocol definition)
9. $TLF_{ISR,SCAI}$; the composite of cardiac death, TV-$MI_{ISR,SCAI}$ or ID-TLR

Note: In the XIENCE ISR analysis population, TV-MI_{ISR} and TV-$MI_{ISR,SCAI}$ include MI events with confirmed target vessel involvement and indeterminate vessel MI events.

Procedures

The procedures for the ISR analysis population are the same as for the full ILUMIEN IV population.

Statistical Considerations

The hypothesis for the XIENCE ISR analysis is as follows:
H_0: $TLF_{ISR} \geq PG$
H_a: $TLF_{ISR} < PG$,

[redacted] The null hypothesis will be tested using a one-sided alpha of 2.5%.

[redacted]

[redacted]

For subjects with multiple target vessels, TLF_{ISR} in any vessel with at least one XIENCE stent implanted on an ISR target lesion constitutes an endpoint event.

The primary endpoint TLF_{ISR} is assessed to evaluate the safety and effectiveness of XIENCE in ISR lesions. This endpoint must be met to demonstrate success for XIENCE in ISR lesions.

[redacted]

Details on subgroup analyses of the XIENCE ISR primary endpoint TLF_{ISR} can be found in the separate Statistical Analysis Plan (SAP).

Other Study Considerations

Unless otherwise noted in this appendix, study conduct for the ISR analysis population is the same as for the full ILUMIEN IV population. This consideration applies to risks and benefits, investigator records and reporting, adverse events, clinical data handling, monitoring, compliance, suspension or premature termination of the clinical investigation, ethical considerations, clinical investigation conclusion, publication policy and results reporting on clinicaltrials.gov website.

[redacted]

Appendix G: References

[redacted]

[redacted]