Investigational Plan

A Clinical Evaluation of the Medtronic Resolute Onyx Zotarolimus-Eluting 2.0 mm Stent

RESOLUTE ONYX 2.0 mm Clinical Study

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Investigational Device:	Medtronic Resolute Onyx Zotarolimus-Eluting Coronary Stent System
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A Clinical Evaluation of the Medtronic Resolute Onyx Zotarolimus-Eluting 2.0 mm Stent

1.2 Objective

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1.3 Design

Single arm, open label multicenter trial

1.4 Study Device

Medtronic Resolute Onyx 2.0 mm Zotarolimus-Eluting Coronary Stent System (Resolute Onyx 2.0 mm stent)

1.5 Endpoints

1.5.1 Primary Endpoint

Target Lesion Failure (TLF) at 12-months post-procedure, defined as Cardiac Death, Target Vessel Myocardial Infarction (TVMI) (Q wave or non-Q wave) or Target Lesion Revascularization by percutaneous or surgical methods.

1.5.2 Key Secondary Clinical Endpoints

- Cardiac Death
- Target Vessel Myocardial Infarction (TVMI)
- Cardiac Death and TVMI
- Major Adverse Cardiac Event (MACE)
- Target Lesion Failure (TLF)
- Target Vessel Failure (TVF)
- Stent Thrombosis (ST)

1.5.3 Secondary Imaging Endpoint

- Ischemia assessment per Myocardial Perfusion Imaging (MPI) for subjects who had MPI at baseline and consent to a follow up MPI

1.5.4 Secondary Angiographic Endpoints

- Late Lumen Loss (LLL)
- Binary Angiographic Restenosis (BAR) rate (defined as ≥ 50% diameter stenosis (DS))
- Percent Diameter Stenosis (% DS)

1.6 Subject population

At least 100 subjects with ischemic heart disease due to *de novo* stenotic lesions within native coronary arteries that meet the eligibility criteria and sign the informed consent form will be asked to participate in this trial. All subjects who consent will be asked to participate in the 13 month angiographic subset until at least 20 subjects have been enrolled in this subset. Subjects may receive treatment in up to two lesions, if the lesions are located in separate target vessels. Core size lesions should be treated with the currently approved Resolute Integrity stent.

The trial will be conducted at a maximum of 25 investigational sites within the United States (US) and Japan. Sites are allowed to enroll a maximum of 20 subjects per site or until study enrollment has been completed, whichever comes first. The expected time of participation in the trial for each subject is three years.

1.6.1 Key Inclusion Criteria

- Subject has clinical evidence of ischemic heart disease. For single vessel disease: stable or unstable angina alone is sufficient. For multi-vessel treatment: a positive functional study or FFR to demonstrate functional need in 2.0 mm small vessel.
- Subject has either a single target lesion suitable for treatment with a Resolute Onyx 2.0 mm stent, or two target lesions located in separate target vessels with at least one suitable for treatment with a Resolute Onyx 2.0 mm stent

See Section 4.4 for a detailed description for all Inclusion Criteria.

1.6.2 Key Exclusion Criteria

- Evidence of an acute MI within 72 hours of the intended trial procedure
- Planned PCI of any vessel within 30 days post-index procedure and/or planned PCI of the target vessel(s) within 12 months post-procedure. (No staged procedures).

  Note: Refer to Table 2 in Section 4.4.5 for additional procedure criteria for planned PCI of the target and other (non-target) vessel(s).

See Section 4.4 for a detailed description for all Exclusion Criteria.

1.7 Schedule of Follow up Assessments

Subject Contact (the subject will be assessed by telephone, e-mail, and/or office visit) at:

- 30 days
- 6 months (subjects that did not have baseline MPI performed)
- Annually 12 months, 2 and 3 years (all subjects)

Clinic Visit (the subject must return to the same investigational site where the index procedure was performed) at:

- 6 months (MPI assessment – subjects with baseline MPI performed and consent to follow-up MPI only)
- 13 Months (angiographic assessment – 2.0 mm Angio subset subjects only)

- Angiography should be performed for any post-procedure clinical event (e.g., MI) to determine if the event is attributable to the target vessel or a non-target vessel. The reason for any repeat angiography (either clinically driven or non-clinically driven) must be documented on the CRF.

Revascularization should only be conducted when ischemic symptoms are found by an objective measurement and stenosis alone does not justify revascularization.

1.8 Statistical Methods

The primary safety endpoint of Target Lesion Failure (TLF) at 12 months post-procedure will be compared to a performance goal derived from outcomes of other Drug Eluting Stents (DES). The TLF performance goal of 19% at 12-months is based on US approved 2.25 mm drug-eluting stent data. The RESOLUTE ONYX 2.0 mm Study design with 100 subjects yields more than 80% power, assuming a one-sided type 0.05 level of significance and 10% loss to follow up.

2.0 INTRODUCTION

2.1 Background

Drug eluting stents have demonstrated superiority over bare metal stents in small vessels[1,2,3] and have been shown to be most effective in reducing restenosis in high risk populations, such as those with small reference vessel diameters[4,5]. A large meta-regression analysis of 31 randomized trials has demonstrated that the clinical benefit of DES increases as the risk profile of the subject increases, without affecting safety[6]. Therefore, the greatest benefit in reducing revascularizations and most cost-effective use of DES are seen in challenging lesions, such as small vessels[7]. Accordingly, Medtronic Vascular has developed a Resolute Onyx 2.0 mm device specifically for the treatment of small stenotic coronary arteries.

Currently, there are approved 2.0 mm bare metal stents, but no approved 2.0 mm DES in the US. A clinical trial is being conducted to demonstrate that the Resolute Onyx 2.0 mm TLF rate is significantly lower than the performance goal estimated from the DES TLF rate in the treatment of small vessel lesions. The successful demonstration of a TLF significantly below the DES TLF Performance Goal would additionally be significantly below the estimated 12-month TLF rates for BMS and POBA in small vessel stenotic coronary disease.

2.2 Study Device Name and Description

The investigational device being evaluated in this clinical trial is the Medtronic Resolute Onyx 2.0 mm Zotarolimus-Eluting Coronary Stent System.

The following is a summary of the Resolute Onyx Stent System. More detailed information regarding clinical indications, contraindications, warnings and precautions, preclinical testing and materials in contact with tissues or body fluids, can be found in the 'Instructions for Use' (IFU).

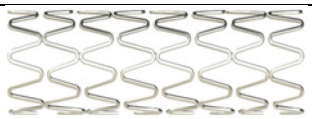
The Medtronic Resolute Onyx Zotarolimus-Eluting Coronary Stent System is comprised of four main components:

1. Stent Platform- Onyx Bare Metal Stent
2. Stent Delivery System - Resolute Onyx Delivery System RX
3. Zotarolimus – Anti-proliferative drug component/active pharmaceutical ingredient
4. Polymer – BioLinx™ Polymer System

2.2.1 Stent

The Resolute Onyx stent is similar in design to the Resolute Integrity stent and utilizes the same continuous sinusoid manufacturing technology.

Table 1: Resolute Onyx Stent Platform

Resolute Onyx	
Material Composition	Cobalt Alloy-shell Platinum/Iridium- core
Appearance	

The stent is manufactured from a composite wire which has an outer shell and an inner core. The outer shell which is in contact with the vessel is of the identical cobalt chromium alloy used for the Resolute Integrity stent. The inner core material is a Platinum/Iridium alloy intended to enhance radiopacity. The stent design has been modified slightly to provide a lower crossing profile and thus, improved deliverability over predicate products.

2.2.2 Stent Delivery System

The Medtronic Resolute Onyx Zotarolimus-Eluting Coronary Stent System consists of a balloon-expandable intracoronary drug-eluting stent pre-mounted on a Rapid Exchange (RX) stent delivery system. The delivery system has two radiopaque markers to aid in the placement of the stent during fluoroscopy and is compatible with 0.014 inch (0.36 mm) guidewires and 5 Fr (1.42 mm/0.056 in) minimum inner diameter guide catheters. The Resolute Onyx RX delivery system (Figure 1) has an effective length of 140 cm.

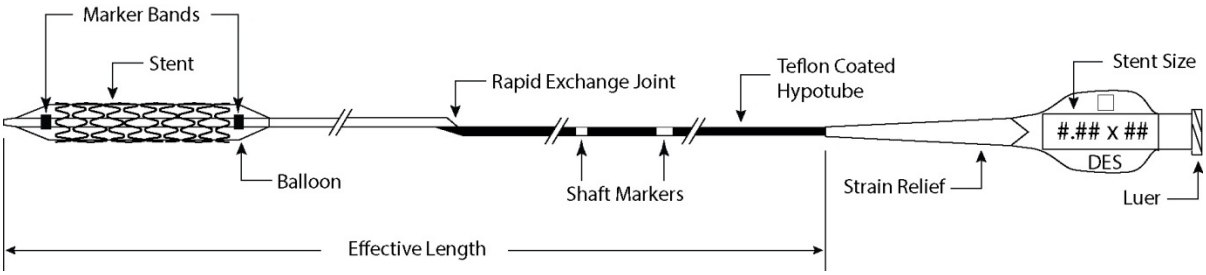


Figure 1: Resolute Onyx RX Delivery System (with Stent)

2.2.3 Zotarolimus Drug Substance

The therapeutic agent utilized in the Medtronic Resolute Onyx Zotarolimus-Eluting Coronary Stent System is zotarolimus, a licensed proprietary chemical entity from Abbott Laboratories, and is also identical to the predicate Endeavor Resolute and Resolute Integrity products. Zotarolimus is a tetrazole-containing macrocyclic immunosuppressant. The suggested mechanism of action of zotarolimus is to bind to FKBP12, leading to the formation of a trimeric complex with the protein kinase mTOR (mammalian target of rapamycin), inhibiting its activity. Inhibition of mTOR results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control. The zotarolimus drug in the Resolute Onyx Stent is intended to reduce the incidence of restenosis in coronary interventions. The Resolute Onyx

Stent has a nominal drug dose of approximately 1.6µg zotarolimus per mm^2 of the stent surface, which is identical to that of Endeavor Resolute and Resolute Integrity.

2.2.4 BioLinx Polymer

The Resolute Onyx stent is comprised of a bare metal stent with a Parylene C primer coat and a coating that consists of a blend of the drug zotarolimus and the BioLinx polymer system. BioLinx is a blend of the Medtronic proprietary components C10 (a copolymer of butyl methracrylate and vinyl acetate) and C19 (a terpolymer containing hexyl methacrylate, vinyl pyrrolidinone, and vinyl acetate), and PVP (polyvinyl pyrrolidone). The Resolute Onyx stent uses the same drug coating formulation, drug dose density and spray processing steps as the predicate Resolute Integrity product.

2.3 Intended Use

The Resolute Onyx 2.0 mm Stent System is intended to improve coronary luminal diameters in subjects with symptomatic ischemic heart disease due to *de novo* stenotic lesion(s) contained within a vessel diameter that allows the use of a 2.0 mm diameter stent.

3.0 CLINICAL TRIAL OBJECTIVES

The purpose of this trial is to assess the safety and efficacy of the Medtronic Resolute Onyx 2.0 mm Zotarolimus-Eluting Coronary Stent System for the treatment of *de novo* lesions in native coronary arteries with a reference vessel diameter (RVD) that allows the use of a 2.0 mm stent.

3.1 Primary Endpoint(s)

Target lesion failure (TLF) at 12-months post-procedure, defined as cardiac death, target vessel myocardial infarction (TVMI) (Q wave or non-Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods.

3.2 Key Secondary Endpoint(s)

Secondary endpoints of this trial include the following:

Clinical Endpoints:

- Acute Success (Device, Lesion, Procedure)
- The following secondary endpoints will be assessed at hospital discharge, 30 days, 6 months, and 12 months post-procedure, and annually thereafter through year 3:
    - Cardiac Death
    - Target Vessel Myocardial Infarction (TVMI)
    - Cardiac Death and TVMI
    - Major Adverse Cardiac Event (MACE)
    - Defined as death, myocardial infarction (Q wave and non-Q wave), emergent coronary bypass surgery, or clinically-driven repeat target lesion revascularization by percutaneous or surgical methods
    - Target Lesion Failure (TLF)
    - Target Vessel Failure (TVF)
    - Stent Thrombosis (ST)

Imaging Endpoint:

- The following secondary endpoint will be assessed at 6 months for subjects who received Myocardial Perfusion Imaging (MPI) per standard care at baseline:
    - Percentage of Myocardium with Reversible Ischemia per Myocardial Perfusion Imaging

Other clinical parameters of stress testing will be collected at baseline and at follow-up testing to assess change following the stenting procedure. These parameters include stress induced angina symptoms, incidence of ST-depression, and exercise capacity.

Angiographic Endpoints:

- The following Angiographic Endpoints will be assessed at 13 months post-procedure (for at least 20 subjects):
    - Late Lumen Loss (LLL)
    - Binary Angiographic Restenosis (BAR) rate (defined as >50% diameter stenosis (DS))
    - Percent Diameter Stenosis

4.0 CLINICAL TRIAL DESIGN

The Medtronic RESOLUTE ONYX 2.0 mm Clinical Trial is a single arm, open label, multi-center trial enrolling at least 100 subjects with ischemic heart disease attributable to stenotic lesions of the native coronary arteries that are amenable to percutaneous treatment with a Resolute Onyx 2.0 mm stent. At least 20 subjects will be enrolled to receive an angiographic follow up at 13 months.

Subjects may receive treatment of one or two lesions, one lesion per target vessel, for a maximum of two target vessels. Only one lesion may be treated in a single target vessel. All treatment with the study stents is to be performed during a single index procedure. Refer to Table 2 for additional stenting criteria.

In the event of one lesion to be treated with a 2.0 mm study stent and another lesion to be treated with a core size (2.25 mm - 4.0 mm) Resolute Integrity stent, the subject should be treated first with the core-sized stent. If the treatment of the first lesion fails or if the subject becomes unstable *before* a 2.0 mm study stent is attempted (stent introduced into guide catheter), the subject will not be enrolled, will not be followed, and will not be included in the primary analysis of this trial. Another subject should be enrolled to replace this subject for the primary analysis. If the treatment with the 2.0 mm study stent is attempted (stent introduced into guide catheter) but not implanted, the subject will be considered part of the Intention-to-Treat population (ITT) and will be followed through the 12 month endpoint and will be included in the primary analysis of this trial.

For subjects who have more than one lesion planned for treatment, a positive functional study or FFR should be performed in the vessel expected to receive the 2.0 mm study stent to demonstrate the functional need for treating such a lesion.

4.1 Location

The trial will be conducted within the United States and Japan at a maximum of 25 investigational sites.

4.2 Number of Subjects

At least 100 subjects will be enrolled in the trial.

4.3 Clinical Trial Duration

The trial will be conducted to allow data collection and analysis for a minimum of 3 years from enrollment of the final subject or until the trial has been formally terminated.

4.4 Subject Selection

All subjects presenting to the cardiac catheterization laboratory for possible interventional treatment are potential candidates. Those subjects who sign the Institutional Review Board (IRB) approved informed consent and subsequently fulfill all inclusion criteria and no exclusion criteria will be enrolled in the trial.

Screening of candidates for this trial should include assessment of the need for anticipated treatment of other target vessel lesions likely to be needed within 12 months post-procedure. Candidates in whom it is likely that other obstructive lesions will require treatment within the target vessel(s) within 12 months post-procedure should not be enrolled in this trial, as assessment of key safety endpoints will occur at 12 months post-procedure.

Per intent-to-treat principles (ITT), subjects who did not have a study stent (Resolute Onyx 2.0 mm stent) implanted but a study stent was introduced into the guide catheter will be followed through 12 months.

4.4.1 General Inclusion Criteria

Subject must meet ***all*** of the following criteria to be eligible for treatment in the trial:

1. Subject is ≥ 18 years old 1[1]
2. Subject is an acceptable candidate for percutaneous coronary intervention (PCI), stenting, and emergent coronary artery bypass graft (CABG) surgery
3. Subject has evidence of ischemic heart disease. For single vessel disease: stable or unstable angina alone as clinical evidence is sufficient. For multi-vessel treatment: a positive functional study or FFR to demonstrate functional need in 2.0 mm small vessel.
4. Female subjects of childbearing potential must have a negative pregnancy test within 7 days before the trial procedure
5. Subject or subject's legal representative has been informed of the nature of the trial and agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective investigational site
6. Subject agrees to comply with specified follow-up evaluations and to return to the same investigational site where the procedure was performed if participating in the angiographic subset

4.4.2 Angiographic Inclusion Criteria

The subject and each target lesion/vessel must meet all of the following angiographic criteria for the subject to be considered for inclusion in the trial:

1. The subject requires treatment of either:
   a. A single target lesion amenable to treatment with a 2.0 mm stent

      OR

   b. Two target lesions located in separate target vessels, with at least one of the target lesions amenable to treatment with a 2.0 mm study stent
2. Target lesion(s) must be *de novo* lesion(s) in native coronary artery(ies)
3. Target lesion(s) treated with a 2.0 mm stent must be ≤ 27 mm in length

[1] ≥20 years old if in Japan

4. Target lesion(s) must have a stenosis of ≥ 50% and < 100%
5. At least one target vessel(s) must have a reference vessel diameter (RVD) ≥ 2.0 mm and < 2.25 mm by visual estimate
6. Target vessel(s) must have a thrombolysis in myocardial infarction (TIMI) flow ≥ 2

   Note: Measurements may be made by careful visual estimate, on-line QCA, or IVUS.

4.4.3 General Exclusion Criteria

Subjects will be excluded from the trial if ***any*** of the following criteria are met:

1. Known hypersensitivity or contraindication to aspirin, heparin and bivalirudin, thienopyridines, cobalt, nickel, platinum, iridium, chromium, molybdenum, polymer coatings (e.g. BioLinx) or a sensitivity to contrast media, which cannot be adequately pre-medicated
2. History of an allergic reaction or significant sensitivity to drugs such as zotarolimus, rapamycin, tacrolimus, everolimus, or any other analogue or derivative
3. Platelet count < 100,000 cells/mm³ or > 700,000 cells/mm³, or a white blood cell (WBC) count < 3,000 cells/mm³ within 7 days prior to index procedure
4. Serum creatinine level > 2.5 mg/dl within 7 days prior to index procedure
5. Evidence of an acute MI within 72 hours of the trial procedure
   a. Q wave myocardial infarction (QWMI);

      OR

   b. Elevated cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the upper reference limit (URL) and with at least one of the following:
      - Symptoms of ischemia
      - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)
      - Development of pathological Q waves in the ECG
      - Imaging evidence of new loss of viable myocardium or new regional wall

   Note: Subjects with evidence or suspicion of an acute MI (per Investigator or Sub-Investigator determination) must have cardiac enzyme results reviewed prior to enrollment.
6. Previous percutaneous coronary intervention (PCI) of the target vessel(s) within 9 months prior to the procedure

   Note: Refer to Table 2 in Section 4.4.5 for criteria of previous PCI to the target and other (non- target) vessel(s).

7. Planned PCI of any vessel within 30 days post-index procedure and/or planned PCI of the target vessel(s) within 12 months post-procedure (no staged procedures)

   Note: Refer to Table 2 in Section 4.4.5 for additional procedure criteria for planned PCI of the target and other (non-target) vessel(s)

8. During the index procedure, the target lesion(s) requires treatment with a device other than percutaneous transluminal coronary angiography (PTCA) prior to stent placement (including, but not limited to, cutting/scoring balloon, atherectomy, laser, thrombectomy, etc.)
9. History of a stroke or transient ischemic attack (TIA) within the prior 6 months
10. Active peptic ulcer or upper gastrointestinal (GI) bleeding within the prior 6 months
11. History of bleeding diathesis or coagulopathy or will refuse blood transfusions
12. Concurrent medical condition with a life expectancy of less than 12 months
13. Any previous treatment of the target vessel(s) for restenosis, including brachytherapy
14. Currently participating in an investigational drug or another device trial that has not completed the primary endpoint or that clinically interferes with the current trial endpoints; or requires coronary angiography, IVUS or other coronary artery imaging procedures

    Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.

15. Documented left ventricular ejection fraction (LVEF) < 30% at the most recent evaluation
16. Inability to comply with the required trial antiplatelet regimen (see Section 5.3)

4.4.4 Angiographic Exclusion Criteria

Subjects will be excluded from the trial if ***any*** of the following criteria are met (for subjects with two target lesions, both target lesions/vessels must not meet any of the criteria below):

1. Target lesion(s) are located in native vessel(s) distal to anastomosis with a bypass graft (including but not limited to saphenous vein graft or a left/right internal mammary artery (LIMA/RIMA)) with more than 40% diameter stenosis anywhere within the graft

   Note: A target lesion distal to a graft may be accessed through the graft.

2. Previous stenting in the target vessel(s) within 9 months prior to procedure; previous stenting in the target vessel(s) ≤ 15 mm from the target lesion(s)
3. Target vessel(s) has/have other lesions with greater than 40% diameter stenosis based on visual estimate or on-line QCA
4. The target vessel(s) has/have evidence of thrombus
5. The target vessel(s) is/are excessively tortuous (two bends > 90º to reach the target lesion)

6. The target lesion(s) has/have any of the following characteristics:
    a. Lesion location is aorto-ostial, or within 5 mm of the origin of the left anterior descending (LAD) or left circumflex (LCX)
    b. Involves a side branch > 2.0 mm in diameter
    c. Is at or distal to a > 45º bend in the vessel
    d. Is severely calcified
7. Unprotected left main coronary artery disease (an obstruction greater than 50% in the left main coronary artery)

4.4.5 Criteria for Additional Procedures

Only one target lesion per target vessel for a maximum of two target vessels may be treated during the trial index procedure. Any other lesion in the target vessel(s) can only be treated after 12 months post-procedure. Any lesion in other (non-target) vessels can be treated after 30 days post-procedure with a Resolute Integrity Stent (preferred) or any approved stent. The criteria for pre and planned post-procedure interventions in the target vessel(s) and other (non-target) vessels are provided in Table 2.

Table 2: Previous and Additional Procedure Criteria

Time Point	Target Vessel(s)	Non-target Vessel(s)
Prior to Index		
> 9 months pre-procedure	Any approved treatment, provided:	> 9 months pre-procedure
9 months to > 30 days pre- procedure	No PCI	Any approved treatment
30 days to > 24 hours prior to index procedure	No PCI	Any bare metal stent provided: - No MACE events resulted if ≤ 30 days from the index procedure - Two post-procedural serial CK-MB measures below the upper limits of normal if ≤ 72 hours
≤ 24 hours prior to index procedure	No PCI	No PCI
Post Index		
< 30 days post-procedure	No PCI*	No PCI**
> 30 days to 12 months post-procedure	No PCI**	Resolute Integrity (preferred) or any approved treatment
> 12 months post-procedure	Resolute Integrity (preferred) or any approved treatment for the intended indication	Resolute Integrity (preferred) or any approved treatment for the intended indication

* In case of acute/subacute closure (within 30 days post procedure) the target lesion(s)/segment(s) should be treated with the study device.
** If deemed medically necessary by the Investigator, the subject should receive any necessary treatment

5.0 TRIAL PROCEDURES

5.1 Screening and Baseline

5.1.1 Screening

All patients evaluated for potential PCI of the coronary arteries should be screened for trial eligibility. A qualified member of the investigational site's research team will review the patient's medical history and screen for trial eligibility. A screening failure case report form (eCRF) will be provided to the site to maintain a record of each patient screened by the site along with the reason(s) for trial exclusion.

5.1.2 Consent

All subjects must complete the consent process **prior** to undergoing any trial related procedures and prior to receiving any trial related medications. Sites must comply with 21 CFR 50 and local IRB policies for obtaining informed consent.

In advance of the consent discussion, the subject should receive the Institutional Review Board (IRB) approved Subject Informed Consent Form. During the consent discussion the investigator or his/her designee (only in geographies where allowed) must fully inform the subject of all pertinent aspects of the trial. If a subject is illiterate, an impartial witness must be present during the entire informed consent discussion. All items discussed in the Subject Informed Consent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable. Consent forms should be made available in subject's native language.

Neither the investigator, nor the investigation site staff shall coerce or unduly influence a subject to participate or to continue to participate in the clinical trial. The informed consent process shall not appear to waive the subject's rights.

When the subject decides to participate in the clinical trial, the site's current IRB and Medtronic approved Informed Consent Form must be signed and personally dated by the subject (or their legally authorized representative) and investigator/or designee. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the Subject Informed Consent Form was accurately explained and clearly understood by the subject, and that informed consent was freely given.

After all persons have signed and dated the Informed Consent Form, the investigator/or designee must provide the subject with a copy of the signed and dated Subject Informed Consent Form. The consent process should be documented in the subject's medical record.

5.1.3 Revisions in Subject Informed Consent Form

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the trial. The investigator or designee should inform the subject in a timely manner.

Medtronic will revise the written Subject Informed Consent Form whenever new information becomes available that may be relevant to the subject's confirmed participation in the trial. The

revised information will be sent to the investigator for approval by the IRB. After approval by the IRB, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

5.2 Clinical Laboratory Procedures & Tests

The clinical procedures that must be performed and laboratory tests that must be drawn for all subjects prior to the stenting procedure are listed below and in Table 3. The results for the procedures and tests required to assess subject eligibility for enrollment (white blood cell (WBC) count, platelet count, creatinine, creatine kinase (CK), Troponin, ECG and pregnancy test (if applicable)) must be obtained and reviewed prior to enrollment.

1. ***Within 7 days prior to the procedure***
   a) A laboratory panel including: a white blood cell count (WBC), platelet count, and creatinine.
   b) A pregnancy test (serum or urine) for women of childbearing potential
   c) A 12-lead ECG
2. ***Within 72 hours prior to the procedure***
   a) Creatine kinase and troponin

   Note: If it is not standard hospital practice to measure CK values, CK-MB values are sufficient. All subjects should have Troponin values.

Table 3: Schedule of Treatments and Assessments

Event	Index Hospitalization					Follow-up Assessments				
	Screening/Pre-Procedure			Proced.	Post-Proced.[1]	30 Day	6 Month	12 Month	13 Month	24, 36 Months
	Screen	Prior to procedure within:				Subject Contact[2]	Subject Contact[2] or Clinic Visit[5]	Subject Contact[2]	Clinic Visit	Subject Contact[2]
		7 days	72 hours							
Informed Consent signed	X									
Medical and cardiac history	X									
Angina status	X				X	X	X	X	X	X
Pregnancy test[3]		X								
Creatinine		X								
WBC with Plts		X								
12 lead ECG		X			X Within 24 hours					
CK[6] and Troponin			X		X 1st: >3hrs 2nd: >4 hrs after 1st, < 24 hrs					
MPI[5]							X			
QCA				X					X[4]	
AE monitoring				X	X	X	X	X	X	X SAEs only
Antiplatelet medications	X Within 24 hours				X	X	X	X	X	X

1. End of procedure is defined as removal of the guide catheter
2. Subject contact includes phone call, email or clinic visit
3. For women of childbearing potential only
4. 2.0 mm Angio Subset only
5. Clinical visit for MPI assessment required for subjects that received an MPI at baseline and agree to do a follow-up MPI
6. If it is not standard hospital practice to measure CK values, CK-MB values are sufficient. All subjects should have Troponin values.

5.3 Medication

All subjects will receive aspirin (a minimum of 75 mg daily, within 24 hours prior to the procedure) and a market approved antiplatelet loading dose within 24 hours prior to the procedure or immediately post procedure (within 30 minutes of last catheter removal). If the subject has taken at least 3 doses of antiplatelet/thienopyridine within 72 hours prior to the procedure, no loading dose is required.

During the index procedure, heparin or bivalirudin will be administered as per hospital standard of care. A GP IIb/IIIa receptor blocker may be administered at the Investigator's discretion.

The use of low molecular weight heparin (e.g., Enoxaparin) is not allowed during the index procedure for this trial and/or at a therapeutic dose (1 mg/kg) within 24 hours prior to procedure.

Following the procedure, subjects will receive a minimum of 75 mg of aspirin daily indefinitely and a market approved thienopyridine daily for a minimum of 6 months in all subjects, and up to 12 months in subjects who are not at high risk of bleeding, per the ACC/AHA/SCAI guidelines[49].

A market approved antiplatelet (clopidogrel, prasugrel, ticagrelor, ticlopidine, etc) should be administered to the subject.

It is important that the subject is compliant with the post-procedural antiplatelet recommendations. Premature discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to enrollment in this trial, if a surgical or dental procedure is anticipated that would require early discontinuation of antiplatelet therapy, the Investigator and subject should carefully consider whether participation in the trial and the associated recommended antiplatelet therapy is the appropriate choice. Following enrollment, should a surgical or dental procedure be recommended, the risks and benefits of the procedure should be weighed against the possible risk associated with interruption or premature discontinuation of antiplatelet therapy.

Subjects who require interruption or premature discontinuation of antiplatelet therapy secondary to significant active bleeding, should be monitored carefully for cardiac events and, once stabilized, have their antiplatelet therapy restarted as soon as possible, per the discretion of their treating physicians.

All antiplatelet/anticoagulant, proton pump inhibitors, beta blockers, ace inhibitors, cox 2 inhibitors, glycoprotein inhibitors, statins, diabetic medications will be documented on the CRF from 24 hours pre-procedure through the 12 month follow-up assessment. Use of antiplatelet/anti-coagulant therapy will be documented throughout the 3 year follow-up period, including any interruptions (temporary stop and restart).

Table 4 summarizes the trial required regimen for antiplatelet medication for subjects enrolled in the trial.

Note: medications and dose as market approved in geography

Table 4: Concomitant Medication Regimen

Time Point	Medication	Regimen
Prior to Procedure	Heparin* or bivalirudin	As needed
	Aspirin	A minimum of 75 mg daily (within 24 hours prior to procedure)
	Clopidogrel/Plavix, Prasugrel/Effient, Ticagrelor/Brilinta, or Ticlopidine/Ticlid or any market approved antiplatelet indicated.	Loading dose within 24 hours prior to procedure or immediately post procedure (within 30 minutes of last catheter removal) No loading dose is required if the subject has taken at least 3 maintenance doses within 72 hours prior to the procedure
During Procedure	Heparin* or bivalirudin	To maintain adequate anticoagulation
	Intracoronary nitroglycerin	50-200 µg prior to stenting and post-intervention angiograms
	GP IIb/IIIa receptor blocker	Use at Investigator's discretion
Post-Procedure	Heparin* or bivalirudin	As needed
	Aspirin	A minimum of 75 mg daily indefinitely
	Clopidogrel/Plavix, Prasugrel/Effient, Ticagrelor/Brilinta or Ticlopidine/Ticlid or any market approved antiplatelet indicated	A minimum of 6 months in all subjects, and up to 12 months in subjects who are not at high risk of bleeding

* The use of low molecular weight heparin is not allowed during the index procedure and/or at a therapeutic dose (1 mg/kg) within 24 hours prior to procedure

5.4 Procedure

Subject preparation and the treatment of the target lesion(s) will be in accordance with standard hospital policy for the care of interventional cardiology subjects unless otherwise specified in this Investigational Plan.

The stenting procedure should be performed according to the IFU for the Resolute Onyx stent and if applicable, the Angiographic Core Lab procedures in Appendix 7.

All standard ancillary devices (*e.g.*, guidewires, sheaths/guiding catheters, pre-dilatation balloons, etc.) used during the preparation and procedure should be used in accordance with the manufacturer's instructions.

5.4.1 Subject Preparation and Angiography

The procedures below will be followed for subject preparation and baseline angiography:

1. Using standard procedures for balloon angioplasty, an introducer sheath of at least 6 French will be introduced using the standard approach (either transfemoral, transradial, or brachial).

   The guiding catheter used during the stent procedure must be 6 French or larger and the guide wire diameter must not be larger than 0.014 in (0.36 mm).

2. Heparin or bivalirudin, with or without a GP IIb/IIIa receptor blocker, will be administered and supplemented as needed to maintain anticoagulation throughout the procedure.
3. Following an intracoronary injection of nitroglycerin, baseline angiography of the vessel(s) will be performed in at least 2 near-orthogonal views that show the target lesion(s) free of foreshortening or vessel overlap, using a 6 French or larger guide catheter (see Appendix 7).

5.4.2 Target Lesion Pre-Treatment

The target lesion(s) must be pre-dilated with standard percutaneous transluminal balloon angioplasty. ***In accordance with the Instructions for Use, this trial does not allow for direct stenting of the target vessel(s).***

Attention must be paid to the pre-dilatation technique in order to avoid balloon injury to any segment of the vessel that will not be entirely covered by the stent ("geographical miss").

Pre-dilatation must be performed using a balloon with the following three characteristics:

1. For lesions treated with a 2.0 mm stent, the pre-dilation balloon used must be ≤ 1.75 mm in diameter.
2. A length matching or shorter than the lesion length to be dilated (to avoid dilatation of the vessel wall adjacent to the stent)
3. A length shorter than the stent to be implanted

The use of other therapy (e.g., cutting balloons, atherectomy, laser, thrombectomy, etc.) is not allowed.

5.4.3 Enrollment

All subjects who meet general eligibility requirements will be asked to participate. Subjects will be considered enrolled into the trial after the following criteria have been met:

1. The signed informed consent has been obtained
2. The study stent (Resolute Onyx 2.0 mm stent) is introduced into the guide catheter

In cases where the procedure is stopped prior to the study stent being delivered into the guide catheter (e.g., subject becomes unstable, power outage, equipment issues, etc.), the subject will not be considered enrolled and will be replaced.

Subject enrollment and stent use information will be submitted to the sponsor on the eCRF within 1 working day or as soon as source documents are available.

5.4.4 Stenting Procedure

The aim is to maintain a homogeneous treatment strategy, and therefore all lesions should be treated with Resolute Integrity (2.25 mm - 4.0 mm) or Resolute Onyx (2.0 mm) stents. Potential interaction with other drug-eluting stents or coated stents has not been evaluated, and should be avoided.

A stent length should be selected so that the lesion can be covered with a single stent in order to avoid the use of multiple stents. Careful stent sizing is important to successful stenting. In general, the stent size should be chosen to match the diameter of the reference vessel and to correspond with the length of the lesion. The appropriate Resolute Onyx Stent size selected for the target lesion must be ≥ 3 mm longer than the lesion length in order to provide 1.5 mm of stent coverage on either side of the lesion.

The stent system will be prepared according to the Resolute Onyx Stent System IFU. The prepared delivery system will be advanced over the guide wire, through the guiding catheter to the target lesion site. The stent will be positioned across the lesion and placement will be confirmed by fluoroscopic angiographic test injections. Deployment of the stent should then be performed in accordance with the IFU.

Available Resolute Onyx 2.0 mm stent sizes are listed in Table 5.

Table 5: Resolute Onyx 2.0 mm Stent Size Matrix

Nominal Expanded Inner Diameter (mm)	Stent Length (mm)						
	8	12	15	18	22	26	30
2.0	✓	✓	✓	✓	✓	✓	✓

Post-dilatation may be performed at the Investigator's discretion with appropriately sized (length and diameter) non-compliant balloon to assure that the stent is in full contact with the vessel wall. ***Do not use the stent delivery balloon for post-dilatation.***

For subjects with planned treatment of two lesions, ***the first lesion must be treated successfully and the subject must be clinically stable before treatment of the second lesion is attempted.***

Successful treatment of the first lesion is defined as:

- <10% residual diameter stenosis result is achieved (visual assessment)
- TIMI 3 flow is present post treatment
- No evidence of dissection (NHLBI Type C, D, E or F), thrombus or distal embolization at the first study lesion site post-treatment.

Prior to attempted treatment of the second study lesion, subjects must be clinically stable without angina or ECG changes consistent with coronary ischemia. If the subject is not clinically stable, or shows signs or symptoms of possible coronary ischemia following treatment of the first study lesion, treatment of the second lesion should be deferred, if possible. Subsequent treatment of the second lesion should be with a study stent if performed during the trial index procedure. If the second lesion requires treatment after the index procedure, a non-study stent must be used.

For subjects with planned treatment of only one lesion but during the procedure a second lesion meeting trial criteria is identified, a Resolute Integrity (2.25 mm - 4.0 mm) or Resolute Onyx (2.0 mm) stent should be used if stenting is needed and treatment cannot be deferred. If the lesion does not meet trial criteria, a non-study stent should be used if stenting is needed and the lesion will be considered a non-target lesion for purposes of analysis.

5.4.5 Bailout

Bailout procedures should be avoided unless required for subject safety. If bailout procedures are performed, justification should be documented on the CRF.

If a subject in the trial experiences a major dissection or an occlusive complication (as evidenced by decreased target vessel flow, chest pain, or ischemic electrocardiogram (ECG) changes which do not respond to standard rescue techniques), bailout procedures may be performed. For these events occurring during the study procedure, additional stenting with Resolute Integrity (2.25 mm - 4.0 mm) or Resolute Onyx (2.0 mm) stents may be employed as a bailout treatment.

In this trial, the target lesion(s) is/are to be selected with the intent to cover each lesion with a single stent. If incomplete coverage occurs during the procedure, additional stenting with study stents may be employed to provide complete coverage.

It is recommended to overlap the Resolute Onyx stents 1-2 mm to avoid the potential for gap restenosis.

5.4.6 Treatment Failure

Following subject enrollment, study stent(s) that enter the guide catheter and fail to be implanted at the intended location are considered treatment failures and will be recorded in the eCRF. In the event of a failure to implant at least one study stent, the Investigator may choose to treat the target lesion(s) with any approved stent. Treatment failures will be followed-up for safety purposes through 12-months and will be included in the intent-to-treat (ITT) population. The subject will undergo the follow-up assessments listed in Section 5.6 through the 12 month follow-up assessment.

> *Note: Damaged or failed Resolute Onyx Stent Systems (including ancillary devices) must be returned to the Medtronic Product Experience Management Department per instructions provided by Medtronic.*

5.4.7 End of Procedure

Upon procedure completion, an intracoronary injection of nitroglycerin must be administered and final angiography of the vessel(s) performed in the same two near-orthogonal views that were taken at baseline, showing the target lesion(s) free of foreshortening or vessel overlap, using a 6 French or larger guiding catheter (see Appendix 7).

The end of the procedure is defined as the time the guide catheter is removed from the subject. If the subject is returned to the procedure room and a guiding catheter is reinserted and a dilatation is performed, this should be considered a repeat intervention.

All adverse events that occur during the procedure must be recorded on the eCRF, including but not limited to dissections, acute closures, etc.

5.5 Post-Procedure to Hospital Discharge

5.5.1 Subject Management

Immediately after the procedure the following will be performed:

1. Heparin or bivalirudin (as market approved by geography) should be discontinued
2. Vascular sheaths should be removed according to standard hospital practice
3. Approved vascular closure devices may be used at the discretion of the Investigator in accordance with the manufacturer's instructions

5.5.2 Clinical and Laboratory Procedures

The following clinical and laboratory procedures will be performed:

1. Qualified study staff at the investigational site will assess the subject's clinical status (including angina) prior to discharge and record any adverse events.
2. Qualified study staff at the investigational site will review the follow-up requirements with the subject to help ensure compliance with the follow-up schedule. Telephone numbers and/or e-mail address should be obtained from the subject to ensure the ability to contact him or her at the required follow-up times. These phone numbers should include all home numbers, work numbers and primary physician numbers. A phone number of a relative or friend should also be requested.

5.5.3 Cardiac Biomarkers

Creatine Kinase (CK) enzyme and troponin will be measured post-procedure following removal of the last catheter as follows:

- 1st draw: >3 hours, <12 hours post procedure
- 2nd draw: >4 hours after 1st draw, <24 hours post procedure

Cardiac enzymes/biomarkers will be collected if they are related to a trial primary or secondary endpoint, including but not limited to death, (suspected) MI or stent thrombosis. These may include creatine kinase (CK) enzyme, creatine kinase myocardial-band (CK-MB) isoenzyme and troponin.

If it is not standard hospital practice to measure CK values, CK-MB values are sufficient. All subjects should have Troponin values.

5.5.4 ECG

A 12-lead ECG will be performed within 24 hours post-procedure or prior to discharge whichever comes first. Additional 12-lead ECGs are required to document any episodes suspicious of cardiac ischemia.

5.6 Follow-Up Requirements

5.6.1 Follow-up General Requirements

The general requirements for follow-up in this trial include:

1. Enrolled subjects who received a study stent will be followed for 3 years after the index procedure by authorized study staff at the investigational site. See Table 6 for follow-up assessment requirements.
2. Subjects in the 2.0 mm Angio subset will return to the site where the procedure was performed for a 13-month clinic visit including an angiogram. Other follow-up contacts will be conducted by telephone, e-mail or clinical visit, unless an unscheduled clinic visit occurs during a follow-up window.
3. A missed follow-up assessment will be documented by the investigator and reported in the eCRF, including the reason for the missed follow-up assessment in the subject's file.
4. Clinical assessments (e.g., angina status, use of antiplatelet medication, new and ongoing adverse events; medical, surgical or dental procedures and the interruption, if any, to antiplatelet therapy) must be performed at each follow-up contact and prior to any interventional procedure (e.g., angiography, PCI) during the 3-year follow-up period.
5. Documentation of referring physicians, general practitioners, cardiologists and family members should be noted to facilitate continued ability to contact a study subject. Any planned long absences by the subject from the area should also be noted.
6. Angiography should be performed for any post-procedure clinical event (e.g., MI) to determine if the event is attributable to the target vessel(s) or a non-target vessel.

The schedule and method for follow-up contacts and windows for each contact is tabled below.

Table 6: Follow-up Contact Requirements

Follow-up Interval	Window	Method*
30 days	± 5 days	Contact
6 months	±14 days	Contact/Clinic Visit**
12 months	± 30 days	Contact
12 month Clinical Follow up must occur at least 1 day prior to the 13 month Angiographic Follow up		
13 months (2.0 mm Angio subset)	± 14 days	Clinic Visit (with Angio)
2 Year	± 30 days	Contact
3 Year	± 30 days	Contact

*Subject contact includes phone call, email or clinic visit
**Clinic visit for subjects with baseline MPI performed, otherwise subject contact visit

5.6.2 Follow-up Data Collection Procedure

The date for the 30-day follow up should be calculated by adding 30 days to the index procedure date (e.g. stent implant on December 5th, 30 day follow-up on January 4th). The dates for the 6 month, 12 month, 13 month and annual (years 2-3) follow-up assessments should be calculated

using the anniversary date of the index procedure (e.g., stent implant on December 5th, 6 month follow-up on June 5th, 12 month and annual thereafter on December 5th). If the procedure was performed on the 31st and the follow-up month has only 30 days, the anniversary should be calculated to the first day of the next month. Visit window calculations will be provided for each subject through the electronic data capture (EDC) system.

Table 7: Subject Follow-up Time Window

Example: Date of implant: 5/DEC/2014

Contact Period	Visit Target Date	Visit Window Dates	
		From	To
30 Day ± 5 days	4/JAN/2015	30/DEC/2014	9/JAN/2015
6 Month ± 14 days	5/JUN/2015	22/MAY/2015	19/JUN/2015
12 Month ± 30 days	5/DEC/2015	5/NOV/2015	4/JAN/2016
13 Month ± 14 days	5/JAN/2016	22/DEC/2015	19/JAN/2016
2 Year ± 30 days	5/DEC/2016	5/NOV/2016	4/JAN/2017
3 Year ± 30 days	5/DEC/2017	5/NOV/2017	4/JAN/2018

5.7 Subject Withdrawal / Removal from the Trial

A trial subject has the right to discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. A withdrawn subject will be treated according to standard of medical care and will not be replaced. Subjects will be included in the analyses up to the time that consent was withdrawn.

If a subject decides to withdraw from the trial, the investigator will document the reason for withdrawal and indicate any rationale for the withdrawal from the trial in the subject's file. Subjects may decide to withdraw from study follow up visits/contacts but consent to continue to allow data collection from their medical records.

Subject Lost-To-Follow-Up (LTFU) should be avoided as much as possible and investigators are urged to do their utmost best to maintain subject follow-up compliance. Contacting the subject's general practitioner or referring cardiologist should be considered in case the subject cannot be reached in order to obtain information about the subject's health status and documented in the subject's file. Continuous attempts throughout the three year follow-up period should be made to contact the subject, the subject's family or referring physician before documenting a subject LTFU. It is recommended that death study databases (SSDI) should be checked before subjects are considered LTFU.

6.0 BENEFITS AND RISKS

6.1 Benefits

The preclinical data from the Resolute Onyx Stent System to date, in conjunction with the extensive body of pharmacokinetic and clinical data from the Resolute Integrity System, demonstrate that the benefits of the Resolute Onyx Stent System outweigh the risks. There are no guaranteed benefits from participation in the trial. The risks of the Resolute Onyx Stent System are provided below.

6.2 Risks

The risks associated with using this device are those associated with standard percutaneous coronary diagnostic and treatment procedures.

Since the Resolute Onyx Stent System is an investigational device, the risks are not entirely known, but are believed to be similar to those that are associated with the standard, customary stenting of a stenosed coronary artery.

All efforts will be made to minimize these risks by selecting Investigators who are experienced and skilled in interventional procedures including stenting, by clearly defining inclusion/exclusion criteria to ensure only appropriate subjects are enrolled, and by ensuring that treatment and follow-up of the subject are consistent with current medical practices.

6.2.1 Zotarolimus

Subjects' exposure to zotarolimus is directly related to the total amount of stent length implanted. The actual side effects/complications that may be associated with the use of zotarolimus are not fully known.

The adverse events that have been associated with the intravenous injection of zotarolimus in humans include but are not limited to:

- Anemia
- Diarrhea
- Dry Skin
- Headache
- Hematuria
- Infection
- Injection site reaction
- Pain (abdominal, arthralgia, injection site)
- Rash

6.2.2 BioLinx Polymer Coating

The types of risks of the BioLinx polymer coating are expected to be no different than those of other stent coatings. These risks may include but are not limited to the following:

- Allergic reaction

- Focal inflammation at the site of stent implantation
- Restenosis of the stented artery
- Percutaneous Coronary Diagnostic and Treatment Procedures

6.2.3 Percutaneous Coronary Diagnostic and Treatment Procedures

Other risks associated with using this device are those associated with percutaneous coronary diagnostic (including angiography and IVUS) and treatment procedures. These risks (in alphabetical order) may include but are not limited to the following:

- Abrupt vessel closure
- Access site pain, hematoma or hemorrhage
- Allergic reaction (to contrast, antiplatelet therapy, stent material, or drug and polymer coating)
- Aneurysm, pseudoaneurysm, or arteriovenous fistula (AVF)
- Arrhythmias, including ventricular fibrillation
- Balloon rupture
- Bleeding
- Cardiac tamponade
- Coronary artery occlusion, perforation, rupture, or dissection
- Coronary artery spasm
- Death
- Embolism (air, tissue, device, or thrombus)
- Emergency surgery: peripheral vascular or coronary bypass
- Failure to deliver the stent
- Hemorrhage requiring transfusion
- Hypotension / hypertension
- Incomplete stent apposition
- Infection or fever
- Myocardial infarction (MI)
- Pericarditis
- Peripheral ischemia / peripheral nerve injury
- Renal Failure
- Restenosis of the stented artery
- Shock / pulmonary edema
- Stable or Unstable angina
- Stent deformation, collapse, or fracture
- Stent migration or embolization
- Stent misplacement
- Stroke / transient ischemic attack
- Thrombosis (acute, sub-acute or late)

7.0 STATISTICAL CONSIDERATIONS

The RESOLUTE ONYX 2.0 mm Clinical Study is a single arm, open label multicenter study enrolling at least 100 subjects with symptomatic ischemic heart disease attributable to stenotic lesions of the native coronary arteries that are amenable to percutaneous treatment with stenting with a Resolute Onyx 2.0 mm stent.

The primary endpoint to be evaluated in this subset is 12 month Target Lesion Failure (TLF) defined as cardiac death, target vessel myocardial infarction (TVMI) (Q wave or non-Q wave), or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods.

7.1 Derivation of Performance Goal

The primary safety endpoint of Target Lesion Failure (TLF) at 12 months post-procedure will be compared to a performance goal derived from outcomes of other Drug Eluting Stents (DES).

Since a 2.0 mm DES has not yet been approved in the US or Japan, the TLF rates at 12 months post-procedure with different 2.25 mm DES stents are selected from literature. The weighted average of TLF rate in those stents is 7.9%.

It is expected that a 2.0 mm stent will have a slightly higher TLF rate because smaller lesions will be treated. Therefore, the expected TLF rate for a 2.0 mm DES is 9.4%.

The performance goal is set at 19%, which is approximately 100% above the expected TLF rate for DES 2.0 mm stent subjects.

7.2 Sample Size Justification

If the 12-month TLF rate of the Resolute Onyx 2.0 mm stent is shown to be significantly less than 19%, then the trial will be considered to have met its primary objective. In other words, the assessment of TLF is a testing with the following null and alternative hypotheses:

$$H_0: \pi \geq 19\% \text{ vs. } H_1: \pi < 19\%,$$

where π is the true Resolute Onyx 2.0 mm stent 12-month TLF rate.

The assessment of the null hypothesis will be carried out at the one-sided 0.05 level of significance. Rejection of the null hypothesis indicates the Resolute Onyx 2.0 mm stent 12-month TLF rate is significantly below 19%.

Accounting for a 10% clinical loss to follow-up and one-sided 0.05 level of significance, a sample size of 100 subjects yields more than 80% power to reject the above null hypothesis in favor of the alternative, assuming the true Resolute Onyx 2.0 mm stent 12-month TLF rate is 9.4%.

7.3 Analysis Populations

Intent-to-Treat (ITT): For this trial, all subjects who sign the written informed consent and also have the study stent (Resolute Onyx 2.0 mm stent) introduced into the guide catheter will be counted in the ITT set, which will be the primary analysis set.

Per-Protocol (PP): The ITT population excluding subjects who do not meet certain key entry criteria. The primary endpoint will also be analyzed in PP population.

7.4 Analysis of the Primary Endpoint

The number and percentage of subjects with 12-month TLF will be provided. A one-sided upper 95% confidence interval of the Resolute Onyx 2.0 mm stent 12-month TLF rate will be calculated through binomial (exact) method. If this upper limit is below 19%, the clinical objective will be considered to have been met.

With regard to clinical outcomes analysis, in subjects receiving treatment of two lesions with a Resolute Onyx 2.0 mm stent, the lesion to be included in the primary analysis, the "analysis lesion", will be randomly selected at the time of analysis. For subjects receiving treatment of a Resolute Onyx 2.0 mm stent and another size stent, the primary analysis will include the lesion treated with the 2.0 mm stent, regardless of the other stent size. A secondary analysis will be conducted for all target lesions.

Statistical non-significance in the primary endpoint for gender comparisons will confirm the homogeneity by gender in this trial.

7.5 Analysis of the Secondary Endpoints

Descriptive statistics for the secondary endpoints will be provided. Categorical variables will be reported using counts and percentages, and continuous variables will be reported by giving the number of known values, the mean, standard deviation, minimum and maximum values. The time-sensitive nature of any response variable may be displayed by using a Kaplan-Meier plot.

7.6 Analysis of Baseline Characteristics

All clinically relevant baseline variables will be tabulated and reported. Categorical variables will be reported using counts and percentages, and continuous variables will be reported by giving the number of known values, the mean, standard deviation, minimum and maximum values.

7.7 Endpoint Analysis and Reporting of Results

All statistical analyses will be performed using SAS for Windows (version 9.1 or higher) or other widely accepted statistical or graphical software. Subject data listings and tabular and graphical presentations of results will be provided.

7.8 Missing Data

Every effort will be undertaken to minimize missing data. In time-to-event outcomes drop-outs will be censored at the time of discontinuation, consistent with the Kaplan-Meier approach.

Unless otherwise specified, no statistical techniques will be used to impute missing data for continuous or categorical outcomes. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

For the primary endpoint, a sensitivity analysis will be conducted to assess the impact of censored data and will include a worst-case analysis.

8.0 CLINICAL EVENTS

8.1 Adverse Events

8.1.1 Definition

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 investigational medical device.

Note 1. This definition includes events related to the investigational 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 investigational medical devices.

A device related AE is defined as any AE for which a causal relationship between the event and the device implantation procedure, the presence of the device, or the performance of the device system, is at least a reasonable possibility (i.e., the relationship cannot be excluded).

A procedure related AE is as any AE associated with the initial placement of the device or any necessary secondary interventions. This includes morbidity associated with either anesthesia or the procedure. This also includes inappropriate subject selection and errors attributed to inappropriate operator techniques, measurements, or judgment.

8.1.2 Reporting Requirements

All non-serious AEs occurring from the time of index procedure through 12 months post-procedure will be recorded in the subject's medical record and reported on the adverse event eCRF within 10 working days after the designated study site personnel first learns of the event. A list of AEs that may be associated with the use of the study device and/or the interventional procedure is provided in the IFU. Each AE must be evaluated to determine if the event meets the definition of serious adverse event (see Section 35). Event, date of onset, duration, and relationship to device will be recorded on the eCRF. AEs will be followed until the event has resolved (in the case of permanent impairment, the event will be followed until it stabilizes and the overall clinical outcome has been ascertained). The AEs must also be reported to the IRB per the institution's policy for reporting AEs.

8.2 Serious Adverse Events

8.2.1 Definition

A serious adverse event (SAE) is defined as an adverse medical occurrence that:

a) led to death

OR

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

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function

OR

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

Note: Planned hospitalization for a pre-existing or a procedure required by the protocol without serious deterioration in health, is not considered a serious adverse event.

The secondary endpoint, MACE (death, Q- or non-Q-wave myocardial infarction, emergent CABG or clinically-driven repeat target lesion revascularization by percutaneous or surgical method), is considered "serious" by this definition.

All serious adverse events (SAE) will be reported for the duration of the trial.

8.2.2 Reporting Requirements

Any AE meeting any of the above criteria for SAE occurring at any time during the trial must be reported by the Investigator or designee, within 3 days after any study site personnel active on the Delegation of Authority first learns of the event. The SAE must also be reported to the IRB per the institution's policy for reporting SAEs.

8.3 Unanticipated Adverse Device Effects

8.3.1 Definition

An unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.3.2 Reporting Requirements

All SAEs will be evaluated by the Medtronic Clinical Operations Safety Department (MCO Safety) to determine if the SAE meets the definition of a UADE. As outlined in Section 8.2, the guideline for reporting all SAEs to Medtronic is within 3 days after the designated study site personnel first learns of the event in order to ensure that Medtronic can meet its regulatory obligations of reporting.

8.4 Device Deficiency, Device Failures and Malfunctions

Manufacturers must report device-related deaths, serious injuries and malfunctions to the FDA and other geography authority whenever they become aware of information that reasonably

suggests that the reportable event occurred (one of their devices has or may have caused or contributed to the event).

8.4.1 Definitions

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

A device failure is defined as the device is used in accordance with the IFU, but does not perform according to IFU and negatively impacts the treatment.

A device malfunction is defined as an unexpected change to the device that is contradictory to the IFU and may or may not affect device performance.

8.4.2 Reporting Requirements

All device failures and malfunctions will be reported on the eCRF within 48 hours of the event and reported to the IRB (if required) within the IRB required timeframe.

In the case of a device failure or malfunction related to the investigational device, the investigational device and any ancillary devices involved in the incident must be returned to Medtronic Product Experience Management per instructions provided by Medtronic.

8.5 Emergency Contact Details

For any trial related emergency, the investigators can contact the Medtronic Clinical Research Specialist assigned to the site. Contact information is listed on the current Study Contact List.

8.6 Time Windows for Expected Completion and Submission of Clinical Events

Table 8: Responsibilities for Submitting Clinical Events

Type of Event	Completed by Site within	Process
Device occurrence reporting (device malfunction or failure)	2 days	Submit within 2 business days after the designated study site personnel first learns of the event and to the IRB (if required) within the IRB required timeframe
Serious adverse events	3 days	Submit as soon as possible but no later than 3 business days after the designated study site personnel first learns of the event and to the IRB within the IRB required timeframe.
UADE	3 days	Submit as soon as possible but no later than 3 business days after the designated study site personnel first learns of the event and to the IRB within the IRB required timeframe.
Adverse events	10 days	Submit to Medtronic as soon as possible but no later than 10 days. Submit to the IRB (if required) within the IRB required timeframe

eCRFs capturing AEs, SAEs, Device Occurrences and UADEs must be submitted via the EDC system. Sites will be contacted and provided a list of documents needed for event review if necessary.

9.0 STUDY MANAGEMENT PROCEDURES

9.1 Investigator and Investigational Site Selection

The primary requirements of Investigator selection for this trial are relevant experience, adequate institutional facilities and equipment, appropriate site research staff to support the conduct of the trial, commitment to safety and adherence to the investigational plan, and patient volume.

Throughout the conduct of the trial, Medtronic and/or its designees will closely monitor compliance with the investigational plan, the applicable laws and regulations, the requirements of the IRB, and the terms of the Clinical Trial Agreement. Medtronic may suspend or terminate the trial prematurely at any site with repeated occurrences of significant non-compliance.

9.2 Investigator Responsibility / Performance

The Investigator is responsible to ensure that all work and services related to this trial described herein, or incidental to those described herein, are conducted in accordance with the highest standards of medical and clinical research practice, the requirements of the IRB, the investigational plan, and the terms of the Investigator Agreement, and all applicable local laws and regulations, U.S. Investigational Device Exemption regulations, including:

- 21 CFR 812: Investigational Device Exemptions
- 21 CFR 50 (Subpart B): Informed Consent of Human Subjects (21 CFR 50.20 General requirements for informed consent)
- 21 CFR 54 (Part 54): Financial Disclosure by Clinical Investigators

Upon completion or termination of the trial, the Investigator will submit a final written report to Medtronic and the IRB as required by the IDE regulations in 21 CFR 812.150. The report will be submitted to Medtronic within three (3) months of completion or termination of the trial and to the local IRB in accordance with the IRB policies and procedures.

The Investigator must maintain a Delegation of Authority Form listing appropriately qualified persons to whom the Investigator has delegated significant trial related duties.

9.3 Training of Investigational Sites

Medtronic and/or its designees are responsible for the training of appropriate clinical site personnel. Medtronic or its designees will present a formal training session to review proper reporting of adverse events, device usage, uniform data collection and compliance with the Investigational Plan (i.e., protocol and consent processes), the device IFU, techniques for the identification of eligible subjects, instructions on data collection, schedules for follow-up, and applicable regulatory requirements. The site Principal Investigator is responsible for key center personnel to be appropriately trained to the tasks they have been delegated. The site Principal Investigator can conduct full trial training for site personnel who were not trained during the Site Initiation Visit. Ongoing assistance regarding completion and submission of eCRFs as well as retraining (if necessary) will be provided by Medtronic and/or its designee.

9.4 Monitoring of Investigational Sites

The trial will be monitored by Medtronic and/or its designee to ensure that high-quality data are obtained in compliance with the clinical investigational plan and appropriate regulatory requirements.

Prior to subject enrollment, a study initiation will be completed with each investigational site. This initiation serves to ensure that Investigators and study personnel are trained appropriately and accept the obligations incurred in conducting this clinical investigation.

Periodic monitoring visits and/or remote reviews will be made at all active investigational sites throughout the clinical trial to ensure that the Investigator obligations are being fulfilled according to all applicable regulations and guidelines.

Upon completion of the clinical trial at a site, a study closeout (remote or on-site) will be performed to ensure that the study related files at the investigational site are up to date and complete and that any outstanding issues have been resolved. Other topics that will be reviewed include: retention of study files, possibility of site audits, publication policy, notifying the IRB of study closure, etc.

9.5 Study Deviations

A study deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the investigational plan, applicable laws or regulations, or the Investigator Agreement.

Regulations require that Investigators maintain accurate, complete and current records, including documentation of any deviations from the investigational plan including the date of and reason for the deviation. The deviations must also be reported to the sponsor in the eCRF.

Investigators are required whenever possible to obtain prior approval from the Medtronic Clinical Research Department before initiating changes in or deviations from the investigational plan, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and maintained in the study files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., subject did not attend scheduled follow-up visit, blood sample lost by laboratory, etc.), the event, however, is still considered a deviation.

Deviations shall be reported to Medtronic regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency. Deviations to protect the life or physical well-being of the subject in an emergency must be reported to Medtronic and the IRB within 5 working days.

Subject specific deviations will be reported on the non-compliance eCRF. Deviations that are not subject specific (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator Agreement, etc.) will be reported to Medtronic in writing. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their IRB requirements.

The center's compliance with the clinical investigational plan will be assessed on an ongoing basis. Corrective and preventive action plans will be developed and implemented to secure compliance. In case of serious noncompliance, the sponsor may decide to stop subject enrollment at a center based on its assessment.

9.6 Device Accountability

Medtronic or its designee will provide investigational devices to all sites. Medtronic Clinical Customer Service (CCS) or Medtronic Japan will be responsible for inventory control. Devices must be stored in a secure area at the site and be accessible and controlled only by the assigned, trained study personnel at the site. The Investigator is responsible for maintaining adequate records of the receipt and disposition of all investigational devices. A device disposition log will be provided for this purpose.

Medtronic and/or its designee will train the Investigator and appropriate site personnel on device-tracking instructions and requirements, which will include the site's record keeping responsibilities of receipt and disposition of all investigational devices shipped to and returned by the site. When the study enrollment is complete, the Investigator shall return any unused devices, opened or unopened, to the designated device distributor.

At the end of enrollment and after the site has returned all remaining device inventory, Medtronic will send a final device reconciliation report to the Investigator or other site personnel designee for review and signature. The site will return the original signed report to Medtronic and maintain a copy of the signed report in their Regulatory Binder.

> *Note: for additional information on shipment, receipt, and return of study devices refer to the device tracking instructions contained in the Manual of Operations binder.*

9.7 Study/Site Suspension or Early Termination

Medtronic, IRB and/or the relevant regulatory authorities have the right to suspend or terminate this study or a participating site at any time and remove study materials from the site as appropriate. A study/site may be suspended or terminated for any of the following reasons.

- Unsatisfactory rate of subject enrollment or compliance to eligibility criteria.
- Repeated noncompliance with the investigational plan.
- Inaccurate, incomplete, and/or untimely submission of data.
- The rate of adverse events in the study or other similar studies indicates a potential health hazard to the subjects caused by the device.
- Inadequate accountability of the investigational device.

In case of study termination subjects may continue to obtain care from their normal provider. In case of site suspension, subjects will be followed by an alternative study site in cooperation with their regular provider.

9.8 Study Close-Out

Upon completion of the clinical study (when all subjects enrolled have completed the follow-up visits and the eCRFs and queries have been completed), Medtronic and/or its designees will

notify the site of closeout and a study closeout visit will be performed. All unused study materials and equipment will be collected and returned to Medtronic and/or its designees or appropriately discarded as per instruction by Medtronic and/or its designee.

9.9 Audits / Inspections

Medtronic initiated audits or regulatory authority initiated inspections at the investigational sites may occur during the course or after completion of the study. In the event that an audit is initiated by Medtronic or a designee (only in geographies where approved), the Investigator shall allow access to the original medical records and provide all requested information. In the event that an inspection is initiated by a regulatory authority, the Investigator shall immediately notify Medtronic of the impending inspection and allow the regulatory body access to the medical records and other information as required by applicable laws and regulations.

9.10 Publication Policies

Publications based on the results of the study will follow the process outlined in the Clinical Research Agreement. A publication committee may be formed to oversee the preparation of manuscripts and identify authors and writers for primary and ancillary publications of the study results.

During the course of or at the conclusion of the study, a multi-center manuscript may be prepared for publication in a reputable peer-reviewed scientific journal. The publication of the results from any single site experience within the study is not allowed until the preparation and publication of the multi-center results has occurred. Exceptions to this rule require the prior written approval of Medtronic.

Additional secondary manuscripts with principal authorship drawn from members of the clinical study or other study related individuals or groups are probable. The analysis of other pre-specified and non-pre-specified endpoints as well as other proposed investigations by members of the clinical study or other study related individuals or groups, will require prior approval by Medtronic. For the purpose of timely abstract presentation and publication, such secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multi-center data will require the approval of Medtronic and Publications Committee.

9.11 Data Management

Medtronic will oversee and/or perform all data management functions. Data management functions include database development, system maintenance, user training, data queries, and report generation.

9.11.1 Case Report Forms (eCRFs)

All required data for this study will be collected on standardized electronic Case Report Forms (eCRFs). A sample copy of the eCRFs is provided in Appendix 4.

9.11.2 Source Documentation

Regulations require that an investigator maintain information in the study subject's medical records to corroborate data collected on the CRF. To comply with these regulatory requirements, the following information will be maintained and made available as required by Medtronic and/or its designees and/or regulatory inspectors. Shadow charts are not appropriate or adequate for source documentation. Complete medical (clinical and hospital) records may include the following documentation:

1. Medical history/physical condition of the study subject before involvement in the study sufficient to verify investigational plan entry criteria and evaluations of prior signs and symptoms
2. Medical record documenting that informed consent was obtained for the subject's participation in the study
3. Description of device implantation procedure (material used, drugs administered during the procedure, date, time, angiographic and clinical findings, etc.)
4. Dated and signed notes for each study subject visit including results of examinations
5. Notations on abnormal lab results and their clinical significance/resolution
6. Dated printouts or reports of special assessments, (e.g., ECG reports, blood tests)
7. Description of adverse events and follow-up of the AEs (at a minimum: event description, onset date, date investigator became aware of the event, duration, relation to study device, treatment, and outcome)
8. Notes regarding concomitant medications taken during the study (including start and stop dates)
9. Study subject's condition upon completion of or withdrawal from the study
10. Other documents and records required by geographies regulation where required

9.11.3 Transmission of Data

Required data will be recorded on the appropriate eCRF at the time of or as soon as possible after the subject visit. The eCRF and any requested supporting source documents must be sent to Medtronic and/or retrieved from the investigator during monitoring visits. Questions about completion of the eCRF may be directed to the Medtronic study team.

9.11.4 Data Queries

During the review of source documents and eCRF at the monitoring visits, any discrepancies noted will be queried by Medtronic or its designee (only in geographies where approved), and must be resolved by the investigational site staff and investigator in a timely manner. In addition, Medtronic or its designee may also generate data queries during routine or remote review of the data. These queries will be sent to the site and must also be resolved in a timely manner.

9.11.5 Time Windows for Completing Case Report Forms and Reports

Table 9: Investigator Reporting Guidance for Submitting Data

Type of CRF/Report/Data	Completed by Site within	Process
Screening failure CRF	7 days	Submit via EDC
Investigational device usage	1 day	Submit within 1 working day.
CRFs (e.g., Inclusion/ Exclusion, Baseline, Follow-up, Report of Noncompliance, Event Forms, Study Exit Form)	7 days or as soon as source documents available	Submit via EDC
Angiographic media	7 days	Site to send media to Core Laboratory within 7 working days of data collection

9.11.6 Electronic Clinical Data Systems

Data will be captured in an electronic data capture system that is 21 CFR Part 11 compliant. Refer to the Manual of Operations for information on the electronic data capture system.

9.12 Record Retention

Records must be maintained by the investigator in compliance with national regulations. Investigator records are subject to regulatory inspection (and Medtronic) and copying, and must be retained for a period of 2 years after the investigation is completed or terminated, or, 2 years after the records are no longer required to support the application to market the device (whichever date is later), or longer if required by applicable local regulations.

The investigator is responsible for the preparation and retention of the records cited below.

- All correspondence with another investigator, IRB, Medtronic, a monitor, or FDA, including required reports and study documents which pertain to the investigation.
- Records of receipt, use, and final disposition of a device.
- Records of each subject's case history and exposure to the device. Case histories include the eCRFs and supporting source data (signed and dated informed consent forms, medical records, e.g., progress notes of the physician, subject's hospital chart, nursing notes).
- The clinical investigational plan, with documents showing the dates of and reasons for each deviation from the protocol.
- Any other records that relevant regulatory authorities require to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

In addition, the Medtronic Vascular Clinical Research Department should be contacted if the Investigator plans to leave the investigational site.

Investigator may withdraw responsibility to maintain records for the time required by the study protocol by transferring custody to another qualified person willing to accept responsibility for them. Medtronic will report this change within 10 days to the relevant regulatory authorities as necessary.

Medtronic will maintain study records under its responsibility indefinitely.

9.13 Investigator Reports

The investigator is responsible for the preparation and submission of the reports cited in the following table. Reports must be prepared in complete, accurate and timely manner. These reports may be subject to regulatory inspection (and Medtronic) and copying, and the retention requirements described above for Investigator Records. In addition to the reports listed in the following table, relevant regulatory authorities or the reviewing IRB may request reports pertaining to any aspect of the clinical study.

Table 10: Investigator Reporting Responsibilities

REPORT	SUBMIT TO	DESCRIPTION/CONSTRAINTS
Unanticipated Adverse Device Effects	Sponsor & IRB	The report must be submitted to Medtronic as soon as possible but no later than 3 working days after the investigator first learns of the effect. Notification to the IRB should be made according to the reporting requirements of the reviewing IRB.
Serious Adverse Events	Sponsor & IRB	The report must be submitted to Medtronic as soon as possible but no later than 3 working days after the investigator first learns of the event. Notification to the IRB should be made according to the reporting requirements of the reviewing IRB.
Adverse Events	Sponsor & IRB	The report must be submitted to Medtronic as soon as possible but no later than 10 working days after the investigator first learns of the event. Notification to the IRB should be made according to the reporting requirements of the reviewing IRB.
Withdrawal of IRB Approval	Sponsor	The investigator must report a withdrawal of the reviewing IRB within 5 working days of the investigator's part of the investigation.
Progress Report	Sponsor & IRB	The investigator must submit this report at least annually for the duration of the study.
Deviation from Investigation Plan (Emergency)	Sponsor & IRB	Notification must be made as soon as possible, but in no event later than 5 working days after the deviation occurred, if the deviation was made to protect the life or physical well-being of a subject in an emergency.
Deviation from Investigation Plan (Other – Non Emergent)	Sponsor & IRB	If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects (and is not an emergency), then the deviation must be approved by Medtronic and the reviewing authority prior to its implementation. If the deviation does not affect these issues (study soundness, rights, safety, etc.) then only Medtronic must approve it, (except in cases which are beyond the control of the investigator—see Section 9.5– Protocol Deviations).
Failure to Obtain Informed Consent	Sponsor & IRB	The Investigator must notify Medtronic and the reviewing authority within 5 working days after device use. The report must include a brief description of the circumstances justifying the failure to obtain informed consent.
Final Report	Sponsor & IRB	This report must be submitted within 3 months after termination or completion of the investigation or the investigator's part of the investigation.

10.0 STUDY COMMITTEES

10.1 Executive Operations Committee (EOC)

The EOC is comprised of the Coordinating Investigator(s) and selected members of the Medtronic Clinical Research Department. Additional individuals may be consulted as appropriate (e.g. Angiographic Core Laboratory personnel, etc.).

The EOC will be responsible for assisting Medtronic with the oversight of the clinical study. This committee will meet periodically by teleconference to discuss subject enrollment and clinical site progress, as well as generally assist sites with the successful conduct of the study. The EOC will be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications.

10.2 Data Monitoring Committee (DMC)

The DMC is composed of at least five members with pertinent expertise (clinicians and at least 1 biostatistician) who are not participants or directly involved in the conduct of the study.

The responsibility of the DMC is to evaluate safety data on an ongoing basis and to advise Medtronic about the continuing safety of the study, in order to ensure the well-being of the current participants and those yet to be enrolled as well as the continuing validity and scientific merit of the study.

Additionally, cumulative reports will be reviewed by the DMC during the follow-up period. Based on the safety data, the DMC may recommend that Medtronic modify or stop the study. All final decisions regarding study modifications or termination will be made by the Medtronic.

10.3 Clinical Events Committee (CEC)

The CEC is comprised of clinicians (interventional and non-interventional) with pertinent expertise who are not participants in the study and who do not have any other real or potential conflicts of interest. The CEC is charged with the development of specific criteria used for the categorization of adverse events and clinical endpoints in the study. Criteria will be established for selected complications and clinical events.

At the onset of the study, the CEC will establish explicit rules outlining the minimum amount of data required and the algorithm followed in order to classify an event.

The Medtronic Clinical Operations Safety Department (MCO Safety) will categorize all clinical events. They will provide this information to the CEC. The CEC will meet regularly to review and adjudicate all events in which the required minimum data are available.

11.0 ETHICAL and REGULATORY CONSIDERATIONS

11.1 Role of Medtronic

As the Sponsor of this clinical study, Medtronic has the overall responsibility for the conduct of the study, including assurance that the study will be conducted according to the International Conference on Harmonization (ICH) GCP guidelines, US FDA, Japan PMDA and local laws. In this study, Medtronic will have certain direct responsibilities and may delegate other responsibilities to consultants and/or contract research organizations.

The principles of the Declaration of Helsinki have all been implemented in this study by means of the subject informed consent process, IRB approval, study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

11.2 General Duties

Medtronic's general duties consist of submitting applications and information to appropriate regulatory authorities, obtaining regulatory and IRB approvals prior to allowing shipment of devices, selecting qualified Investigators, ensuring proper clinical site monitoring, ensuring subject informed consent is obtained and ensuring that the IRB and relevant regulatory authorities are promptly notified of significant new information about the investigation.

Medtronic is responsible for providing quality data that satisfies regulations and informing Investigators, IRB and relevant regulatory authorities of UADEs/SADEs and deviations from the investigational plan as appropriate. The Medtronic Clinical Study Team will provide written progress reports and a final report.

11.3 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification code (subject sequence number) will be assigned and used to allow identification of all data reported for each subject.

Study data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that study data are published.

The study sites in the US must comply with the subject confidentiality provisions of the Health Insurance Portability and Accountability Act (HIPAA) issued by the U.S. Department of Health and Human Services (HHS). Sites should maintain subject privacy in accordance to federal regulations (45 CFR Parts 160 and 164), local regulations, and institutional requirements.

11.4 Supplemental Applications

As appropriate, Medtronic will submit changes in the investigational plan to the appropriate regulatory authorities and to Investigators to obtain IRB re-approval as required.

11.5 Informed Consent and Institutional Review Boards

All subjects must provide written informed consent in accordance with 21 CFR Part 50 and approved by the site's IRB and Medtronic. A copy of the informed consent form template from each site must be forwarded to Medtronic for review and approval prior to submitting it to the IRB. A sample copy of the informed consent form is provided in Appendix 4. Each site must provide Medtronic with a copy of the investigational site's IRB approval letter and the IRB approved informed consent form. Approvals for the continuation of the study at each investigational site must be kept current and notifications forwarded to Medtronic.

12.0 REFERENCES

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13.0 Appendices

Appendix 1: Study Contact Information

Sponsor: - Project & Site Management - Statistical Analysis	Medtronic Vascular 3576 Unocal Place Santa Rosa, CA 95403
Coordinating Investigators:	Matthew J. Price MD, FACC, FSCAI Scripps Green Hospital 10666 North Torrey Pines Road, Maildrop S1056 La Jolla, CA 92037 Shigeru Saito, MD Shonan Kamakura General Hospital 1370-1 Okamoto, Kamakura Kanagawa 247-8533
Clinical Operations: - Data Management - Electronic Data Capture Monitoring - Safety	Medtronic, Inc. Medtronic Clinical Research Institute Strategy and Scientific Operations 710 Medtronic Parkway, LS330 Minneapolis, MN 55432
Product Experience Management:	CVG Product Experience Management, Medtronic Ireland, Parkmore Business Park West, Ballybrit, Galway, Ireland
Angiographic Core Lab:	Beth Israel Deaconess Medical Center, Inc 375 Longwood Avenue, 3rd Floor Boston, MA 02215
Image Transfer:	Intelemage, LLC. 700 W. Pete Rose Way, Suite 436 Cincinnati, OH 45203
Clinical Events Committee: Data Monitoring Committee:	Harvard Clinical Research Institute (HCRI) 930 Commonwealth Avenue, Third Floor Boston, MA 02215

Appendix 2: Acronyms, Abbreviations, and Definitions

Acronym/Abbreviation	Term
% DS	Percent diameter stenosis
ACC	American College of Cardiology
ACT	Activated clotting time
AE	Adverse event
AHA	American Heart Association
©	Copyright
CABG	Coronary artery bypass graft
CCSC	Canadian Cardiovascular Society Classification
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CK	Creatine kinase
CK-MB	Creatine kinase myocardial-band isoenzyme
CRF	Case report form
CRO	Contract Research Organization
DES	Drug eluting stent
DMC	Data Monitoring Committee
DS	Diameter stenosis
ECG	Electrocardiogram
EDC	Electronic data capture
FDA	Food and Drug Administration
FFR	Fractional Flow Reserve
GCP	Good Clinical Practices
GI	Gastrointestinal
HHS	US Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
ICH	International Conference on Harmonization
IFU	Instructions for Use
ITT	Intent-to-treat
IVUS	Intravascular ultrasound
LAD	Left anterior descending coronary artery
LCX	Left circumflex coronary artery
LIMA	Left internal mammary artery
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac event
mg	Milligram
MI	Myocardial infarction
MLD	Minimum luminal/lumen diameter
µg	Microgram
Mm	Millimeter
MPI	Myocardial Perfusion Imaging
NTG	Nitroglycerin

Acronym/Abbreviation	Term
PCI	Percutaneous coronary intervention
Plt	Platelet
PTCA	Percutaneous transluminal coronary angioplasty
QCA	Quantitative coronary angiography
QD	Every day
QWMI	Q wave myocardial infarction
RCA	Right coronary artery
RIMA	Right internal mammary artery
RVD	Reference vessel diameter
RX	Rapid exchange
SAE	Serious adverse event
SD	Standard deviation
TIA	Transient ischemic attack
TIMI	Thrombolysis in myocardial infarction
TLF	Target lesion failure
TLR	Target lesion revascularization
™	Trademark
TVF	Target vessel failure
TVR	Target vessel revascularization
UADE	Unanticipated adverse device effect
WBC	White blood cell
WHO	World Health Organization

Term	Definition
ACUTE CLOSURE	
Acute Closure:	Defined as the occurrence of new (during the procedure) severely reduced flow (TIMI grade 0-1) within the target vessel that persisted and required rescue by stenting or other treatment, or resulted in myocardial infarction or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not mean "no reflow" (due to microvascular flow limitation), in which the epicardial artery is patent but had reduced flow. Abrupt closure also does not mean transient closure with reduced flow in which the index treatment application does reverse the closure.
Subacute Closure:	Defined as abrupt closure that occurred after the procedure is completed (and the subject left the catheterization laboratory) and before the 30-day follow-up evaluation.
Threatened Acute Closure:	Defined as a grade B dissection and ≥ 50% diameter stenosis or any dissection of grade C or higher.

ACUTE SUCCESS

All acute success data will be reported per Medtronic historical protocol definitions and current definitions listed below.

Device Success:

Medtronic historical definition: attainment of < 50 % residual stenosis of the target lesion using only the study device.

Current definition: the attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using the study device only. These measurements will be made by the independent angiographic core laboratory. If the core laboratory is unable to assess the % residual stenosis, the investigator's assessment as recorded in the CRF will be used for the statistical analysis.

Lesion Success:

Medtronic historical definition: attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.

Current definition: the attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method. These measurements will be made by the independent angiographic core laboratory. If the core laboratory is unable to assess the % residual stenosis, the investigator's assessment as recorded in the CRF will be used for the statistical analysis.

Procedure Success:

Medtronic historical definition: attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.

Current definition: the attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method without the occurrence of MACE during the hospital stay. These measurements will be made by the independent angiographic core laboratory. If the core laboratory is unable to assess the % residual stenosis, the investigator's assessment as recorded in the CRF will be used for the statistical analysis.

Device Specific Procedure Success:

Device success and no in-hospital MACE.

ADVERSE EVENT

An adverse event 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 investigational medical device.

Note 1. This definition includes events related to the investigational 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 investigational medical devices.

ANTICIPATED ADVERSE EVENT

Any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject, whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the clinical protocol, predefined in the clinical protocol and/or IFU, that is identified or worsens during a clinical study.

BINARY ANGIOGRAPHIC RESTENOSIS

Defined as ≥ 50% in-stent diameter stenosis at the follow-up angiogram. If an in-stent measurement is not available, the in-lesion diameter will be used.

CALCIFICATION

Calcification is defined as readily apparent radiopacities within the vascular wall at the site of the stenosis and is classified as none/mild, moderate (radiopacities noted only during the cardiac cycle before contrast injection), and severe (radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen).

CANADIAN CARDIOVASCULAR SOCIETY CLASSIFICATION (CCSC) OF ANGINA[49,10]

Class I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
Class II	Slight limitation of ordinary activity. Angina upon walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the first hours after awakening. Angina if walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
Class III	Marked limitations of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.
Class IV	Inability to carry on any physical activity without discomfort. Angina syndrome may be present at rest.

CEREBROVASCULAR ACCIDENT (CVA) (see Stroke)

CLINICALLY-DRIVEN TARGET LESION REVASCULARIZATION (TLR)

Revascularization at the target lesion associated with positive functional ischemia study or ischemic symptoms AND an angiographic minimal lumen diameter stenosis ≥ 50% by QCA, or revascularization of a target lesion with diameter stenosis ≥ 70% by QCA without either angina or a positive functional study.

CLINICALLY-DRIVEN TARGET VESSEL REVASCULARIZATION (TVR)

Revascularization in the target vessel associated with positive functional ischemia study or ischemic symptoms AND an angiographic minimal lumen diameter stenosis ≥ 50% by QCA, or revascularization of a target vessel with diameter stenosis ≥ 70% by QCA without either angina or a positive functional study.

DE NOVO LESION

Defined as a lesion not previously treated.

DEATH

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac.

Cardiac death	Any death due to immediate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death. This includes all procedure related deaths including those related to concomitant treatment.
Vascular death	Death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.
Non-cardiovascular death	Any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

DEVICE RELATED ADVERSE EVENT

A device related adverse event is defined as any adverse event for which a causal relationship between the event and the device implantation procedure, the presence of the device, or the performance of the device system, is at least a reasonable possibility (i.e., the relationship cannot be excluded).

DEVICE SUCCESS

Attainment of < 50 % residual stenosis of the target lesion using only the study device.

DEVICE SPECIFIC PROCEDURE SUCCESS

Device success and no in-hospital MACE.

DIABETES MELLITUS[11]

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both.

Three ways to diagnose diabetes are possible, and each must be confirmed, on a subsequent day, by any one of the three methods given:

1. Symptoms of diabetes plus casual plasma glucose concentration > 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
2. Fasting plasma glucose (FPG) > 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 hours.
3. Two hour post-load glucose (PG) > 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health

Organization (WHO)[12], using a glucose load containing the equivalent of 75 gm anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The third measure, OGTT, is not recommended for routine clinical use.

Medtronic working definition of diabetes mellitus: For the purposes of this trial a subject is considered to have a history of diabetes mellitus if he/she: is taking insulin, is taking oral antidiabetic agents, is on a modified diet to control diabetes mellitus, or has a diagnosis of diabetes mellitus documented in the medical record but is untreated, prior to the index procedure. Subjects who are taking insulin, or both insulin and oral agents, will be classified as insulin dependent. Subjects who are taking oral agents only, a modified diet only, both oral agents and a modified diet, or are currently untreated, will be classified as non-insulin dependent.

DISSECTION, NHLBI (National Heart, Lung, and Blood Institute) CLASSIFICATION[13]

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

EMERGENT BYPASS SURGERY

Defined as coronary bypass surgery performed on an urgent or emergent basis for severe vessel dissection or closure, or treatment failure resulting in new ischemia.

FRACTIONAL FLOW RESERVE

A measurement of blood flow and blood pressure to determine the need for PCI.

INCOMPLETE APPOSITION

Failure of the stent to completely appose to the vessel wall after placement. Defined as one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut in the ultrasound image.

LATE LUMEN/LUMINAL LOSS

Defined as the difference between the post-procedure minimal lumen diameter (MLD) and the follow-up angiography MLD.

LESION CLASS (American College of Cardiology/American Heart Association Class)[14]

Type A Lesions: Minimally complex, discrete (length < 10 mm), concentric, readily accessible, non-angulated segment (< 45°), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, and an absence of thrombus.

Type B Lesions: Moderately complex, tubular (length 10 to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (> 45°, < 90°), irregular contour, moderate or heavy calcification, total occlusions < 3 months old, ostial in location, bifurcation lesions requiring double guidewires, and some thrombus present.

Type B1: One adverse characteristic.

Type B2: Two or more adverse characteristics.

Type C Lesions: Severely complex, diffuse (length > 20 mm), excessive tortuosity of proximal segment, extremely angulated segments > 90°, total occlusions > 3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.

LESION SUCCESS

Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.

MAJOR ADVERSE CARDIAC EVENTS (MACE)

Defined as death, myocardial infarction (Q wave and non-Q wave), emergent coronary bypass surgery, or clinically-driven repeat target lesion revascularization by percutaneous or surgical methods.

MINIMAL LUMINAL DIAMETER (MLD)

The average of two orthogonal views (when possible) of the narrowest point within the area of assessment – in lesion, in stent or in segment. MLD is visually estimated during angiography by the Investigator; it is measured during QCA by the Angiographic Core Laboratory.

MYOCARDIAL INFARCTION (MI)

All myocardial infarction data will be reported per Medtronic historical protocol definitions.

Q wave MI (QWMI): will require one of the following criteria:

Chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC, in the absence of timely cardiac enzyme data.

New pathologic Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC and elevation of cardiac enzymes. In the absence of ECG data the CEC may adjudicate Q wave MI based on the clinical scenario and appropriate cardiac enzyme data.

Medtronic Historical Definition of Non-Q Wave MI (NQWMI): elevated CK ≥ 2X the laboratory upper limit of normal with the presence of an elevated CK-MB (any amount above the laboratory upper limit of normal) in the absence of new pathological Q waves.

Extended Historical Definitions:

I. PCI (PERCUTANEOUS CORONARY INTERVENTION)

Ia. Baseline Biomarkers of Myocardial Damage (CK and CKMB and Trop < 1*URL) *and* not acute MI in progress.

PERIPROCEDURAL <48 HOURS POST PCI
A. New pathologic q waves in ≥ 2 contiguous ECG leads ***AND***: ▪ any CKMB > 1*URL ***or*** ▪ in the absence of CKMB: Troponin > 1*URL ***or*** ▪ in the absence of CKMB and Troponin: CK > 1*URL ***or*** ▪ in the absence of CKMB and Troponin and CK: CEC decision upon clinical scenario B. Appropriate cardiac enzyme data (respecting top-down hierarchy, b1 to b3): b1. CK ≥ 2* URL Confirmed by : ▪ CKMB > 1*URL ***or*** ▪ in the absence of CKMB:, Troponin > 1*URL ***or*** ▪ in the absence of CKMB and Troponin: CEC decision upon clinical scenario ***OR*** b2. In the absence of CK: CKMB > 3*URL ***OR*** b3. In the absence of CK and CKMB: Troponin > 3*URL

Note: URL = upper reference limit, defined as 99th percentile of normal reference range

Ib. If Baseline Biomarkers of Myocardial Damage: CK and/or CKMB > 1*URL *or* acute MI in progress

MYOCARDIAL INFARCTION, RE-INFARCTION (EXTENSION) <48 HOURS POST PCI
A. If CK (or CKMB) from index MI has not yet reached its maximum level: ▪ Recurrent thoracic chest pain or ischemia equivalent >20 minutes (or new ECG changes consistent with MI) ***AND*** ▪ Appropriate cardiac enzyme data: o A rise in CK within 24 hours of the index event >2*URL (confirmed by either CKMB or Troponin > 1*URL) and ≥ 50% above the previous level ***or*** o In absence of CK: a (post PCI) rise in CKMB within 24 hours of the index event >3*URL and ≥ 50% above the previous level or o In absence of CK and CKMB: a (post PCI) rise of Troponin within 24 hours of the index event >3*URL and ≥ 50% above the previous level. B. If elevated CK (or CKMB) following the index MI has peaked ***AND*** CK level has returned < URL then any new rise in: ▪ CK >2*URL(confirmed by either CKMB > URL or Troponin >URL) ***or*** ▪ in the absence of CK: CKMB > 3*URL ***or*** ▪ in the absence of CK and CKMB, Troponin > 3*URL C. If CK (or CKMB) following the index MI has peaked ***AND*** CK level has NOT returned to < URL: ▪ A rise in CK ≥50% above the previous level and > 2 URL confirmed by either CKMB > URL or Troponin > URL. ***or*** ▪ In absence of CK, when CKMB has NOT returned < URL, a rise in CKMB ≥50% above the previous level and > 3 URL. ***or*** ▪ In absence of CK, when CKMB and Troponin has not returned < URL a rise in Troponin ≥ 50% above the previous level and >3*URL

SPONTANEOUS MI >48 HOURS (PCI)
A. Recurrent thoracic chest pain or ischemic equivalent ***AND*** ▪ New pathologic q waves in ≥ 2 contiguous ECG leads ***AND*** any CKMB > 1*URL.***or*** ▪ in the absence of CKMB: Troponin > 1*URL ***or*** ▪ in the absence of CKMB and Troponin: CK > 1*URL ***or*** ▪ in the absence of CKMB and Troponin and CK: CEC decision upon clinical scenario B. Appropriate cardiac enzyme data (respecting top-down hierarchy): b1. CK ≥ 2* URL Confirmed by: ▪ CKMB > 1*URL ***or*** ▪ in the absence of CKMB: Troponin > 1*URL ***or*** ▪ in the absence of CKMB and Troponin: CEC decision upon clinical scenario ***OR*** b2. In the absence of CK: CKMB > 3*URL ***OR*** b3. In the absence of CK and CKMB: Troponin > 3*URL ***OR*** b4. In the absence of CK, CK-MB and Troponin, clinical decision based upon clinical scenario.

II. CABG (CORONARY ARTERY BYPASS GRAFTING)

IIa. Baseline Biomarkers of Myocardial Damage (CK and CKMB and Trop < 1*URL) and not acute MI in progress.

PERIPROCEDURAL <72 HOURS POST CABG
A. New pathologic q waves in ≥ 2 contiguous ECG leads or recurrent signs or symptoms consistent with myocardial ischemia ***AND*** ▪ CK-MB >5x URL ***or*** ▪ in the absence of CKMB: Troponin > 5*URL ***or*** ▪ in the absence of CKMB and Troponin: CK > 5 URL ***or*** ▪ in the absence of CKMB and Troponin and CK: CEC decision upon clinical scenario B. Appropriate cardiac enzyme data ▪ CKMB ≥ 10* URL ***or*** ▪ In the absence of CKMB: Trop > 10*URL. ***or*** ▪ In the absence of CKMB and Troponin: CK > 10*URL

IIb. If Baseline Biomarkers of Myocardial Damage: CK and/or CKMB > 1*URL *or* acute MI in progress

MYOCARDIAL INFARCTION, RE-INFARCTION (EXTENSION) <72 HOURS POST CABG
A. If Peak CK (or CKMB) from index MI has not yet reached its maximum level: ▪ Clinical signs or symptoms consistent with recurrent myocardial ischemia ***AND*** ▪ Appropriate cardiac enzyme data: o A rise in CKMB within 24 hours of the index event >10*URL and ≥ 50% above the previous level. o In absence of CKMB: a rise in Troponin within 24 hours of the index event o >10*URL and ≥ 50% above the previous level. o In absence of CKMB and Troponin: a rise in CK within 24 hours of the index event >10*URL and ≥ 50% above the previous level. B. If elevated CK (or CKMB) following the index MI has peaked ***AND*** CKMB level has returned < URL, any new rise in: ▪ CKMB >10*URL ***or*** ▪ in the absence of CKMB: Troponin > 10*URL ***or*** ▪ in the absence of CKMB and Troponin: CK > 10*URL C. If elevated CK (or CKMB) following the index MI has peaked ***AND*** CKMB level has NOT returned < URL: ▪ A rise in CKMB ≥50% above the previous level and > 10 URL ***or*** In absence of CKMB: a rise in Troponin ≥50% above the previous level and > 10* URL. ***or*** ▪ In absence of CKMB and Troponin: a rise in CK ≥ 50% above the previous level and >10*URL

MYOCARDIAL PERFUSION IMAGING

A type of nuclear stress test used to identify areas of the heart that aren't getting enough blood using radioactive tracers and electrodes.

NO REFLOW

Defined as a sustained or transient reduction in antegrade flow that is not associated with an obstructive lesion at the treatment site.

PERCENT DIAMETER STENOSIS

The value calculated as 100 x (RVD – MLD)/RVD using the mean values from two orthogonal views (when possible) by QCA.

PERFORATION

Perforations will be classified as follows:

Angiographic perforation:	perforation detected by the clinical site or the core laboratory at any point during the procedure.
Clinical perforation:	perforation requiring additional treatment (including efforts to seal the perforation or pericardial drainage), or resulting in significant pericardial effusion, acute closure, myocardial infarction, or death.
Pericardial hemorrhage/tamponade:	perforation resulting in cardiac tamponade.

PROCEDURE SUCCESS

Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.

RESTENOTIC LESION

Defined as a lesion in a vessel segment that has undergone prior percutaneous treatment with or without a stent placement.

REFERENCE VESSEL DIAMETER (RVD)

Defined as the average of normal segments within 10 mm proximal and distal to the target lesion from two orthogonal views using QCA.

SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is defined as an adverse medical occurrence that:

a) led to death

OR

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

1) a life-threatening illness or injury, or
2) a permanent impairment of a body structure or a body function, or
3) in-patient or prolonged hospitalization, or
4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function

OR

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

STENT THROMBOSIS

All stent thrombosis data will be reported per the Academic Research Consortium (ARC) definitions.

Academic Research Consortium (ARC) Definition:

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points as specified below. Time 0 is defined as the time point after the guiding catheter has been removed and the subject has left the catheterization lab.

Timing:

Acute stent thrombosis *	0 – 24 hours post stent implantation
Subacute stent thrombosis *	> 24 hours – 30 days post stent implantation
Late stent thrombosis	> 30 days – 1 year post stent implantation
Very late stent thrombosis	> 1 year post stent implantation

* Acute or subacute stent thrombosis can also be replaced by the term early stent thrombosis.

Three categories of evidence define stent thrombosis: *Definite, Probable, Possible*

1. **Definite** (either by angiographic or pathologic confirmation):
   a. Angiographic confirmation of stent thrombosis is considered to have occurred if:
      i. Thrombolysis In Myocardial Infarction (TIMI) flow is:
         1. TIMI flow grade 0 with occlusion originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus
         2. TIMI flow grade 1, 2, or 3 originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus
      ii. AND at least one of the following criteria has been fulfilled within a 48 hour time window:
         1. New onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes)
         2. New ischemic ECG changes suggestive of acute ischemia
         3. Typical rise and fall in cardiac biomarkers (refer to definition non-procedural related MI).

      *Note: The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is **not** considered a confirmed stent thrombosis (silent occlusion).*
   b. Pathologic confirmation of stent thrombosis:
      Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.
2. **Probable:**

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

   a. Any unexplained death within the first 30 days.

b. Irrespective of the time after the index procedure any myocardial infarction (MI), which 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.

3. **Possible:**

   Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow-up.

STROKE

Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists more than 24 hours.

STUDY DEVIATION

A study deviation is defined as an event where the Investigator or site personnel did not conduct the trial according to the investigational plan, applicable laws or regulations, or the Investigator Agreement.

STUDY STENT

A study stent is defined as the Resolute Onyx 2.0 mm stent.

TARGET LESION

Any lesion treated or attempted to be treated during the study procedure. The target lesion is the treated segment starting 5 mm proximal to the stent and ending 5 mm distal to the stent.

TARGET LESION FAILURE (TLF)

Defined as cardiac death, target vessel myocardial infarction (Q wave and non-Q wave), or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods

TARGET LESION REVASCULARIZATION (TLR)

Repeat PCI or CABG to the target lesion. See also clinically-driven target lesion revascularization.

TARGET VESSEL

The arterial segment and any branches and/or parent vessel that possess the target lesion. For this study, the target vessel can only be the left main (protected), LAD, Cx, RCA. Side branches less than 2.0 mm in diameter will not be considered ‘significant’ and therefore the disease in these vessels will not be considered significant.

TARGET VESSEL FAILURE (TVF)

The composite endpoint comprised of cardiac death, target vessel myocardial infarction, or clinically-driven target vessel revascularization by percutaneous or surgical methods.

Target vessel failure will be reported when ANY of the following events occur:

- Recurrent MI occurs in territory not clearly attributed to a vessel other than the target vessel.
- Cardiac death not clearly due to a non-target vessel endpoint.
- Target vessel revascularization is determined.

TARGET VESSEL MYOCARDIAL INFARCTION (TVMI)

Target-vessel MI is defined as a MI that occurs in a territory that cannot be clearly attributed to a vessel other than the target vessel.

TARGET VESSEL REVASCULARIZATION (TVR)

Repeat PCI or CABG of the target vessel. See also clinically-driven target vessel revascularization.

THROMBOLYSIS IN MYOCARDIAL INFARCTION (TIMI) CLASSIFICATION[15]

TIMI 0	No perfusion.
TIMI 1	Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis for the duration of the cine run.
TIMI 2	Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel.
TIMI 3	Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

THROMBUS (INTRACORONARY)[16]

Non-occlusive thrombus:	Intracoronary thrombus is defined as a (spheric, ovoid or irregular) non-calcified filling defect or lucency surrounded by contrast material (on three 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.
Occlusive thrombus:	TIMI 0 or TIMI 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch).

TOTAL OCCLUSION

A total occlusion is defined as a lesion with no flow (TIMI 0). Total occlusions are usually classified as persisting less than or more than 3 months (chronic total occlusion).

TRANSIENT ISCHEMIC ATTACK (TIA)

A TIA is defined as a focal neurological abnormality of sudden onset and brief duration (lasting less than 24 hours) that reflect dysfunction in the distribution of the effected artery. TIAs include transient monocular blindness (e.g., amaurosis fugax defined as a transient episode of monocular blindness, or partial blindness, lasting ten minutes or less) and transient hemispheric attacks.

UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

An UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

UNSTABLE ANGINA

Per the ACC/AHA 2002 Guideline Update for the Management of Subjects with Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction there are three (3) principal presentations of unstable angina (UA)[17]:

1. Rest Angina. Angina occurring at rest and prolonged, usually >20 minutes.
2. New-onset Angina. New-onset angina of at least CCS Class III Severity.
3. Increasing Angina. Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by greater than or equal to 1 CCS class to at least CCS Class III severity).

Appendix 3: Investigator's Brochure/Report of Prior Investigations

NOTE: Refer to the most current version of the Investigator's Brochure/Report of Prior Investigations sent under separate cover.

Appendix 4: Sample Subject Informed Consent Form

NOTE: Refer to the most current version of the Sample Subject Informed Consent Form and Authorization to Use and Disclose Health Information sent under separate cover.

Appendix 5: Sample Case Report Forms

NOTE: Refer to the most current version of the case report forms sent under separate cover.

Appendix 6: Study Device Instructions For Use

NOTE: Refer to the most current version of the instructions for use sent under separate cover or packaged with the device.

Appendix 7: Angiographic Core Laboratory Procedures

NOTE: Refer to the most current version of the Angiographic Core Laboratory Procedures sent under separate cover.

Appendix 8: Japan specific

NOTE: Applicable to Japan sites only - sent under separate cover.

Appendix 9: Center for Medicare and Medicaid Services (CMS) IDE Study Criteria – Applicable to US sites only

Medicare Beneficiaries

The results of this study are expected to be applicable to a significant number of Medicare beneficiaries based on incidence of cardiovascular disease, number of percutaneous coronary interventions, and number of patients with relevant luminal reference diameters of the culprit coronary artery in this population.

A 2010 report published by the Centers for Disease Control (CDC) found that coronary heart disease was the most common subtype of heart disease hospitalization, representing 42.0 % of all Medicare heart disease hospitalizations.[(1)]

Analyses of percutaneous coronary interventions among Medicare beneficiaries showed the following number of PCI episodes (both admission and non-admission) from 2008 to 2012 [(2)]:

- 2008: 423,789 PCI episodes
- 2009: 426,518 PCI episodes
- 2010: 434,134 PCI episodes
- 2011: 417,963 PCI episodes
- 2012: 401,929 PCI episodes

These numbers are expected to increase over the next 15 years based on the baby boom generation reaching Medicare age, as well as the current incidence of cardiac revascularizations performed on Medicare beneficiaries. [(2)]

With regard to the specific populations that may benefit from the Resolute Onyx 2.0 mm, diameter device, the Journal of the American College of Cardiology published a study showing that among a study of 2,306 patients, 35% (n=813 patients) with a mean age of 65 were found to have a luminal reference diameters of less than or equal to 2.5 mm. [(3)]

Sources:

1. Greer SA, Nwaise IA, Casper ML. *Atlas of Heart Disease Hospitalizations Among Medicare Beneficiaries*. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; Accessed on February 12, 2015 at http://www.cdc.gov/dhdsp/atlas/2010_heart_atlas/docs/executive_summary.pdf)
2. Culler, S et al. "Trends in coronary revascularization procedures among Medicare beneficiaries between 2008 and 2012." Circulation, 2015. Vol 131, Issue 4. pp. 362-370.
3. Schunkert, H. et al. "Implications of Small Reference Vessel Diameter in Patients Undergoing Percutaneous Coronary Revascularization." Journal of the American College of Cardiology, 1999; 34:40-8.